Pathophysiology of Vaso-Occlusion, an Update

Fisiopatologia da Vaso-Oclusão-Atualização

Nicola Conran
Hemocentro/FCM/UNICAMP
Sickle Cell Disease Vaso-occlusion
Basic Pathophysiology of Vaso-occlusion

1) HbS Polymer Formation: RBC deoxygenation
   High intracellular [HbS]
   Low [HbF]
   Low pH

2) Chronic Inflammatory State

3) Increased RBC Transit Time in the Microcirculation:
   Cell-Endothelium adhesion
   Cell-cell aggregate formation
   Abnormal cationic homeostasis
   Abnormal vasoregulation

4) Other factors: Oxidative/nitrostatic stress
   Thrombin formation
Sickle Cell Disease and the Chronic Inflammatory State

Endothelial adhesive interactions

Cellular activation and up-regulation of endothelial adhesion molecules
E-selectin, VCAM-1, ICAM-1

Further adhesion of red cells and leukocytes to endothelium

Endothelial damage by sickled red cells
Ischemia-Reperfusion Injury

Elevation of circulating levels of cytokines and chemokines
IL-1, TNFα, GM-CSF, IL-8
Red Blood Cells and Vaso-occlusion
Red Blood Cells and Vaso-occlusion

- Endothelial Cell
- Fibronectin
- VCAM-1
- Trombospondin
- CD36
- Laminin
- BCAM/LU
- SS RBC

Adapted from Setty et al. (2000) Blood
Augmented leukocyte numbers are associated with increased morbidity and mortality in SCD.

Increased leukocyte numbers are associated with an elevated risk for CVA and acute chest syndrome in young patients.
Endothelial Cell

ICAM-1

Mac-1

neutrophil

ICAM-4

Autologous IgG

Chemotaxis
Leukocytes and Vaso-occlusion

Cremaster muscle preparation in SS mouse

After TNFα stimulation

http://www.mssm.edu/labs/frenette/microcirc.shtml
• **Therapy with hydroxyurea (HU):**  
The benefits of HU are often observed before an increase in HbF production; due to reduction in neutrophil numbers?

• **Eosinophils:** Elevated numbers  
  Increased adhesive properties (FN)
Platelets and Vaso-occlusion

- Platelets circulate in an activated state in SCD
- Increased liberation of β-tromboglobulina, PF-4, TSP, IL-1
- P-selectina, GPIIb/IIIa increased
- Adhesive properties increased
Nitric Oxide (NO) and Vaso-occlusion

- **NO**: signaling gas
  produced mainly by endothelial cells
  half-life of seconds

- **cGMP**: Principal NO second messenger

- **NO**: Essential for vascular hemostasis
  anti-thrombotic
  anti-adhesive
SCD and Reduced NO Bioavailability

• ↓ L-arginine levels

• consumption by ROS

• Scavenging by cell-free hemoglobin – intravascular hemolysis
Scavenging of NO by cell-free hemoglobin

Reduced NO Bioavailability

Reiter et al., Nature Medicine, vol 8, 2002
<table>
<thead>
<tr>
<th>Manifestations of reduced NO bioavailability in SCD</th>
</tr>
</thead>
</table>

- Pulmonary Hypertension
- Priapism
- Leg Ulcer
- CVA
- Renal insufficiency
- Gastrointestinal Pain
Role of cAMP in altered leukocyte function in SCD

cAMP

• Cyclic nucleotide
• Intracellular signaling molecule
• Mediates signaling of hormones, neurotransmitters and cytokines
• Intracellular targets: protein kinase A (PKA), ionic channels, Epac
• Long and short term responses
Role of cAMP in altered leukocyte function in SCD

Leukocytosis

↑ Production de cytokines
GM-CSF  IL-8  IL-6

Vascular Inflammation

Prostaglandin (E1/E2)

↑ Intracellular cAMP

Role of cAMP in altered leukocyte function in SCD

- ↑ Intracellular cAMP
  - ↑ Cellular adhesion
  - Inhibition of cell death
  - ↑ chemotaxis

- Exacerbation of inflammation state
- Vaso-occlusion

---

Effects of Hydroxyurea in the Microcirculation

Cokic et al., Blood, 2006
Therapeutic targets for the prevention and treatment of vaso-occlusion in SCD

**NO donors**

- L-Arginine
- Allopurinol
- Hydroxyurea
- Inhaled nitric oxide
- Inhaled or intravenous nitrite
- Statins

**PKA inhibition?**

**Anti-adhesive therapies, eg. Small molecule cyclic αvβ3 antagonists**

Adapted from Mack & Kato Int J Biochem Cell Biol, 2006
NO Bioavailability
Inflammation
Cell Adhesion
Vasoconstriction

Propagation of the fibrin plaque
Obstruction of rigid RBC
Diminished Blood Flow
Vas-occlusion

Switzer et al., Lancet Neurol 2006; 5:501
Acknowledgments

Prof. Dr. Fernando F. Costa

Andreia Canalli
Carla Franco-Penteado
Carolina Lanaro
Sheley Gambero