Sickle Cell Disease Symposium Connecting inflammatory biomarkers and SCD clinical severity : the lung complications perspective

Marqueurs de l'inflammation et sévérité clinique: le cas des complications pulmonaires

Marthe-Sandrine Eiymo Mwa Mpollo, PhD

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### Sickle Cell Disease (SCD)



### **Treatment strategies**

- Management of vaso-occlusive crisis
- Management of chronic pain syndromes
- Management of chronic hemolytic anemia
- Prevention and treatment of infections
- Management of the complications and the various organ damage syndromes associated with the disease
- Prevention of stroke
- Detection and treatment of pulmonary hypertension

### Beyond RBC sickling, hemolysis other features/organ complications of SCD include





# What is the connection between this single defect in RBC and those multi-organ complications?

Assumptions:

- 1) Produce by sickled red blood cells
- 2) Correlate with the severity of the disease pathophysiology

The Biomarkers Definitions Working Group (2001) defined a biomarker as 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention'.

Rees, British Journal of Haematology 2011 156, 433–445.

### Placenta Growth Factor is produced by immature erythroid and not other hematopoietic cells



"From a clinical perspective, pulmonary complications namely, the acute chest syndrome and pulmonary hypertension — are the most common causes of death in patients with sickle cell disease." Gladwin, NEJM 2008

- Pulmonary hypertension: Incidence is 30% (Gladwin MT et al, 2004).
- Airway hyperreactivity and asthma reported to be 17% to 77% (Boyd JH. et al, 2006)
- Acute Chest syndrome (ACS): with an incidence rate of 50%, ACS is estimated to be responsible for 25% of SCD related deaths (Castro, Blood 1994; Platt, Blood Principles and Practice of Hematology 1995).
- Inflammation: Activated leukocytes have been shown to initiate vaso-occlusion (Wun T. et al, 2001).

Is PIGF a biomarker for pulmonary hypertension (PH)?

### PIGF is elevated in adult patients with SCD and is associated with features of PH.

в



Variable	n	r	р
RBC_COUNT	123	-0.28	0.0017
lemoglobin	123	-0.27	0.0024
Absolute Reticulocyte count	123	0.07	0.4233
.DH	116	0.22	0.0153
SR	115	0.19	0.0465
CRP	114	0.30	0.0012
VBC count	122	0.19	0.0376
Endothelin-1	117	0.24	0.0087
RJV	123	0.38	P<0.0001







Sundaram, Blood 2010

PIGF overexpression in WT mice induces right ventricular hypertrophy and pulmonary hypertension



Sundaram, Blood 2010

Could PIGF be a biomarker for Acute Chest Syndrome (ACS)?

# Leukotrienes: PIGF target genes are strongly associated with ACS

- ACS: lung complication believed to result from vaso-occlusions in the pulmonary circulation
- The leukotrienes, powerful inflammatory molecules, are potent vasoconstrictors in the pulmonary circulation.



# PIGF-induced airway hyper-reactivity is associated with ACS



PIGF inhibition reduces both leukotrienes and airway hyperreactivity, ACS associated features



Eiymo, JCI 2015

### Summary

PIGF, an inflammatory mediator released by the sickle RBC connect the seemingly unrelated many diseases activities in SCD





## Beyond RBC sickling, hemolysis other features/organ complications of SCD include

#### Lung

Acute chest syndrome Airway Hyper-reactivity Pulmonary hypertension Ongoing fibrosis pneumonia

### Heart

Cardiomyopathy Premature coronary and artery disease

### Gallbladder

Gallstones

### **Bones/joints**

Bone marrow hyperplasia Avascular necrosies Dactilytis Osteomyelitis Aplastic crisis

### Vascular damage

Pain

Stroke (brain) Central artery damage Retinal and artery occlusion/ retinopathy

### Spleen

Splenic sequestration of RBC Autosplenectomy Chronic hypersplenectomy Impaired immunity

### Kidney

Hypostenuria Papillary necrosis Renal failure

### **Genitals** Priapism