

Adhésion à l'endothélium dans la drépanocytose

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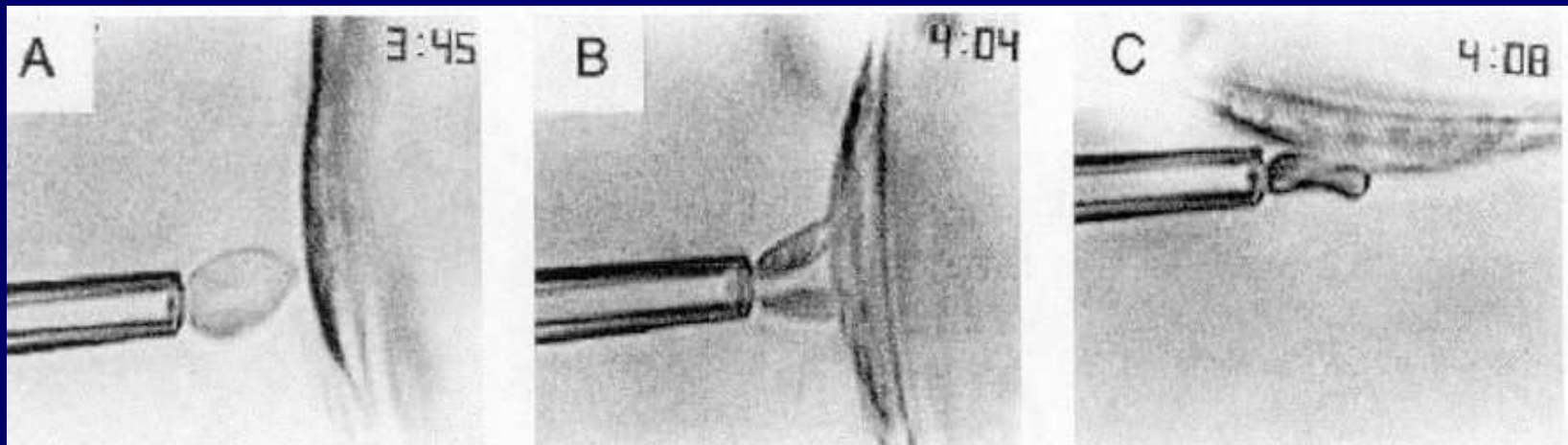
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Centre de Référence des Antilles et de la Guyane



CGRF Marseille 15/17 Octobre 2007

1980s: abnormal adhesion of SS-RBC to the endothelium



Mohandas & Evans, Blood 1984

Hoover R, Rubin R, Wise G, Warren R
Adhesion of normal and sickle erythrocytes to endothelial monolayer cultures.
Blood 1979, 54:872-876

Hebbel RP, Yamada O, Moldow CF, Jacob HS, White JG, Eaton JW
Abnormal adherence of sickle erythrocytes to cultured vascular endothelium: possible mechanism for microvascular occlusion in sickle cell disease.
J Clin Invest 1980, 65:154-160

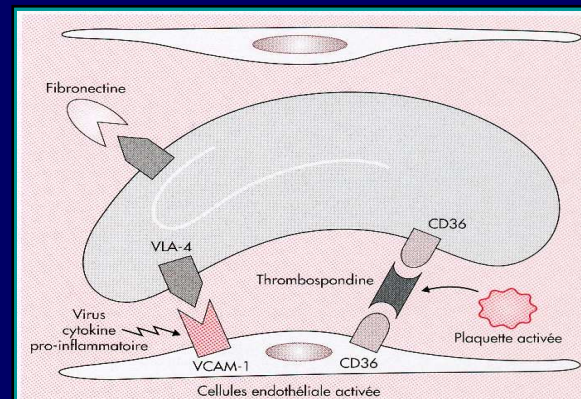
RBC adhesion in SCD

Three questions:

- which vascular territory?
- which red cells?
- what molecular mechanism(s)?

RBC adhesion in SCD

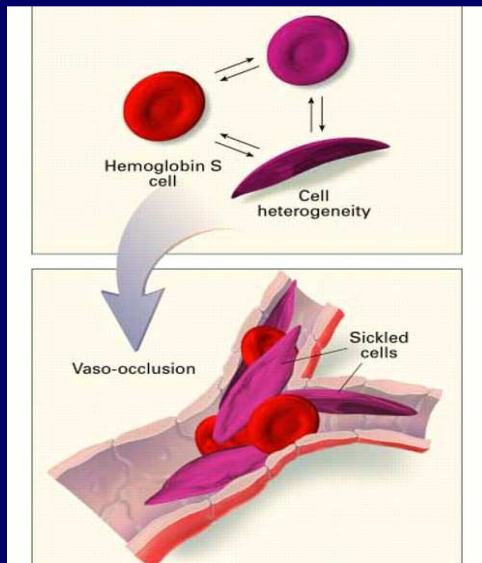
- post capillary veinules
- young RBC / activated endothelium



*Elion & Labie
Hématologie 1998*

- molecular mechanism(s):
 - stress reticulocytes express adhesion molecules normally found on erythroid precursors in the bone marrow (VLA-4 = $\alpha 4\beta 1$ integrin)
 - VCAM-1 is expressed only on an activated endothelium
 - plasma proteins - proinflammatory cytokines

a very needful discovery because:



Steinberg M.H.,
N Engl J Med
1999; 340:1021-1030

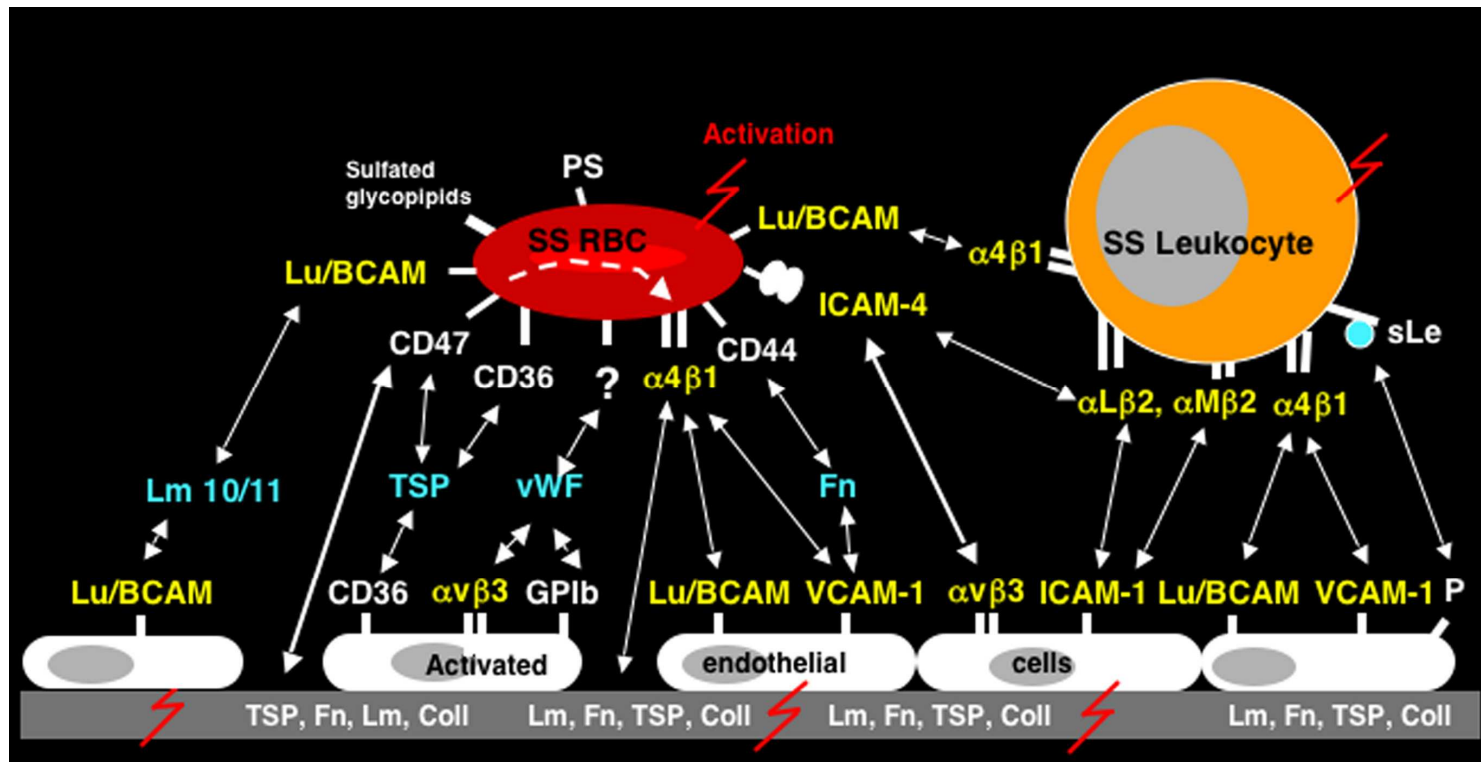
in SCD, the primary physiopathological event is insufficient to explain vasoocclusion since the delay time to HbS polymerization is longer than the time required in the circulation to reoxygenate the blood

thus all mechanisms reducing blood flow may constitute a triggering factor

.... *cell adhesion*

.... *vascular tone*

since then the initial scheme has become notably more complex



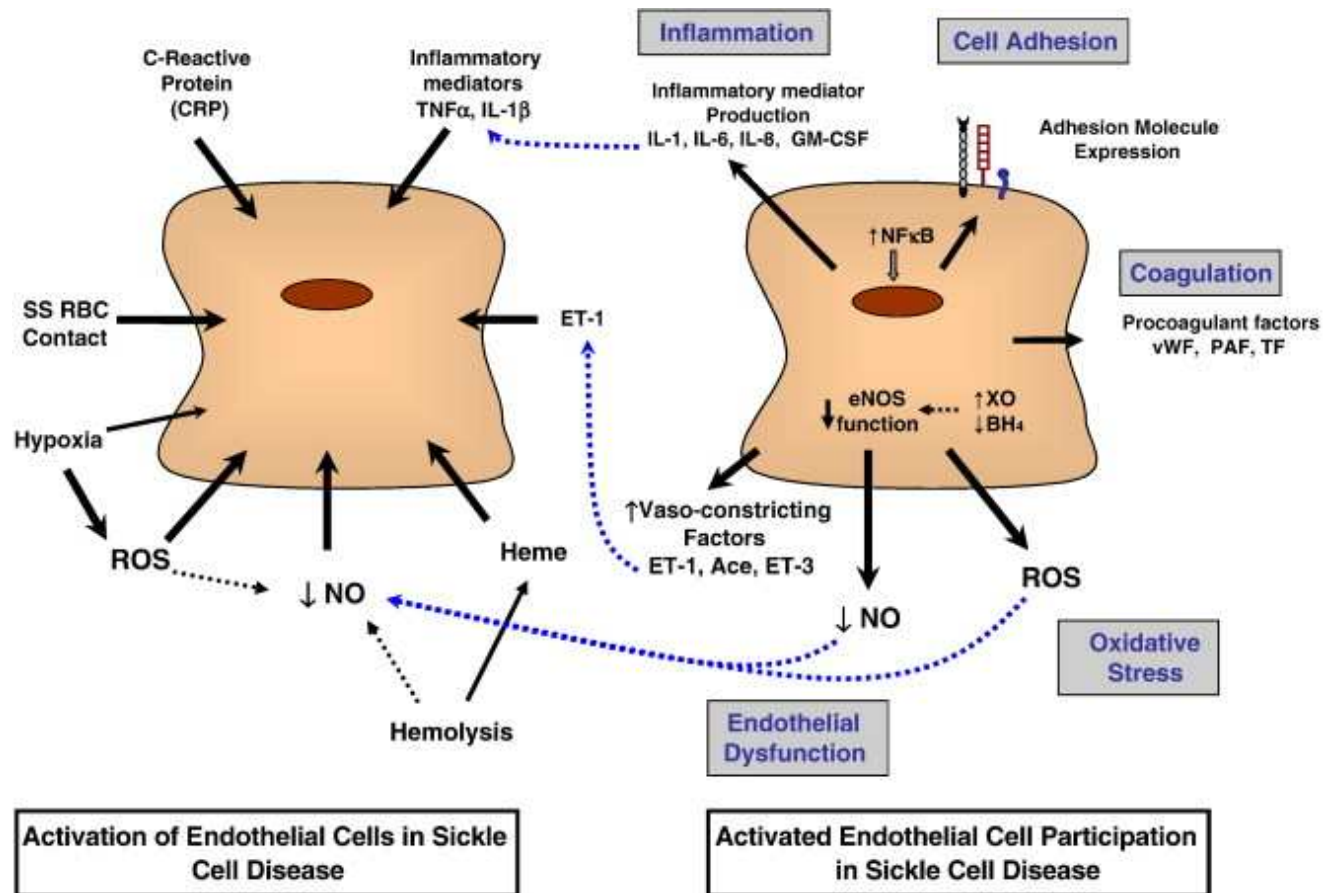
from JP Cartron

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hallmarks:

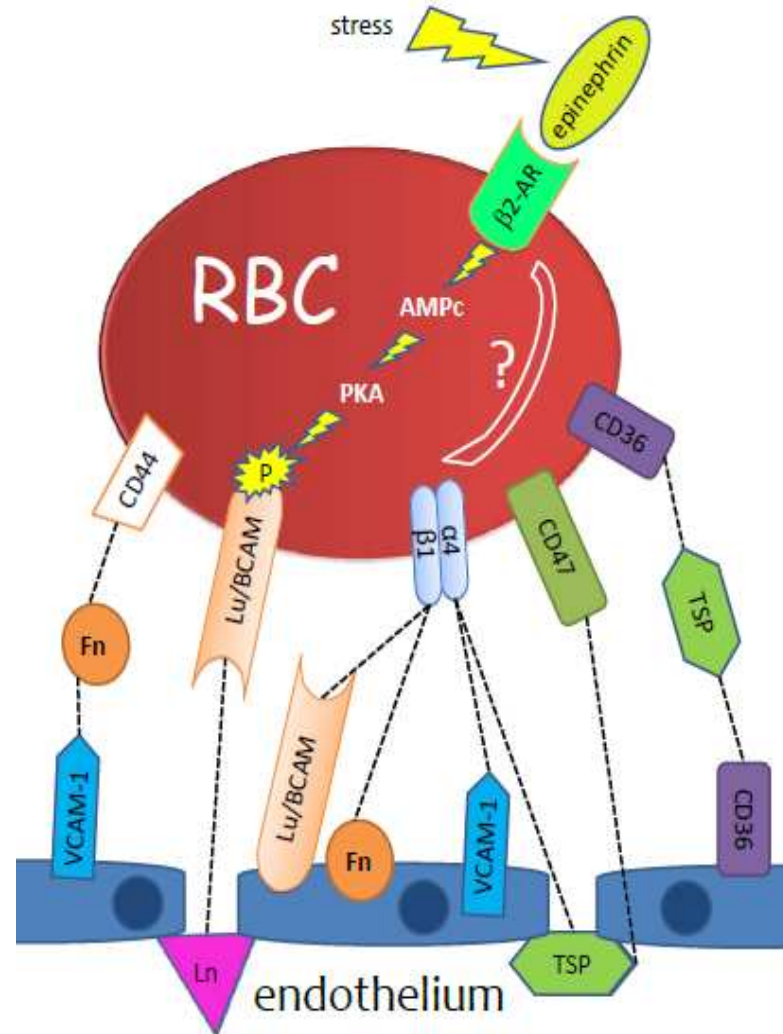
- all the cells present in the vessel are involved
- cell activation is a major contributor

Activated endothelial cells are major contributors to the pathophysiology of SCD



RBC are activable cells

and activation participates to RBC adhesion to the endothelium



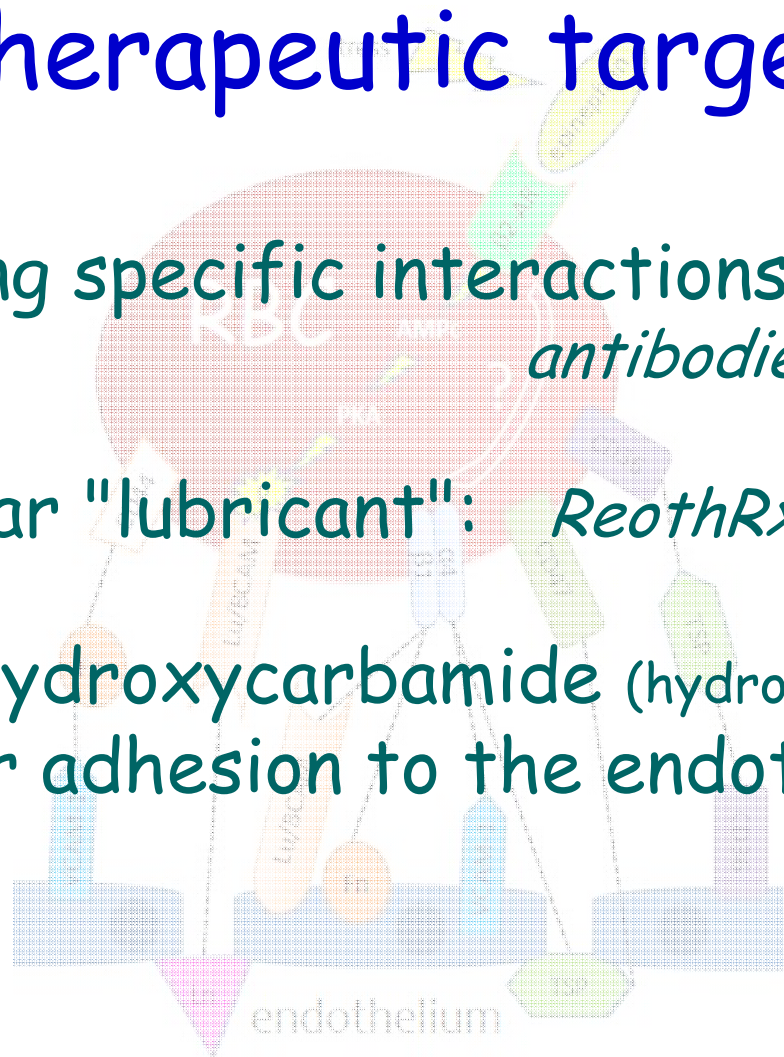
El Nemer, Le Van Kim, Colin
Blood. 2007
Transfus Clin Biol. 2008
Transfus Clin Biol. 2010

RBC adhesion to the endothelium as a therapeutic target?

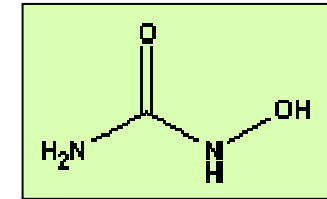
Blocking specific interactions: *antibodies, RGD peptides*

Vascular "lubricant": *ReothRx*

Does hydroxycarbamide (hydroxyurea) affect cellular adhesion to the endothelium?



HYDROXYCARBAMIDE (HC) is the only effective drug in SCD



FDA 1998 (adults)

DROXIA® Bristol-Myers Squibb

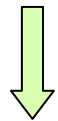
EMA 2007 (adults and children)

SIKLOS® AddMedica

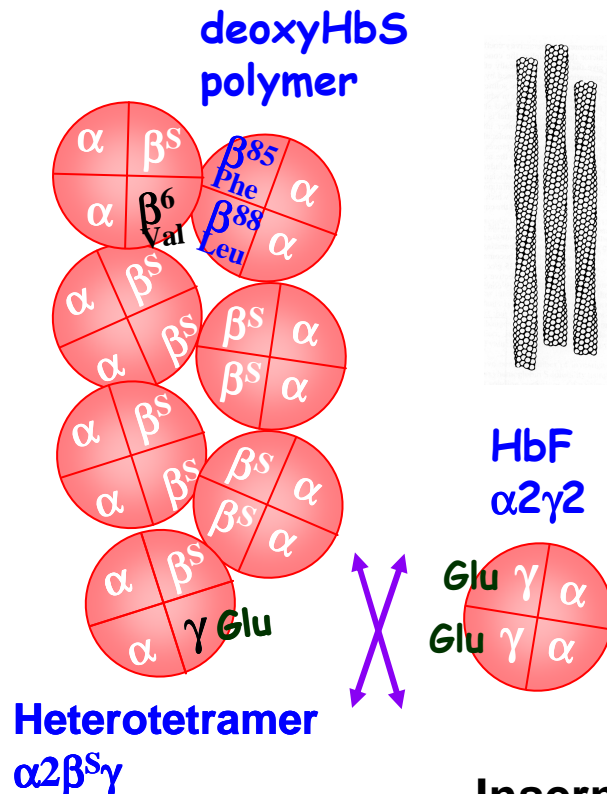
Initial expectation from HC:
increased HbF expression



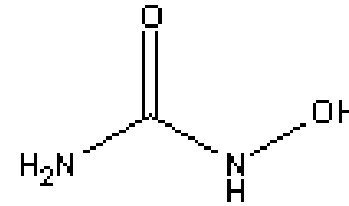
decreased HbS polymerisation



reduced vaso-occlusion



HYDROXYCARBAMIDE & Sickle Cell Disease



⇒ Oral HU : proven efficacy in clinical trials (adults & children)

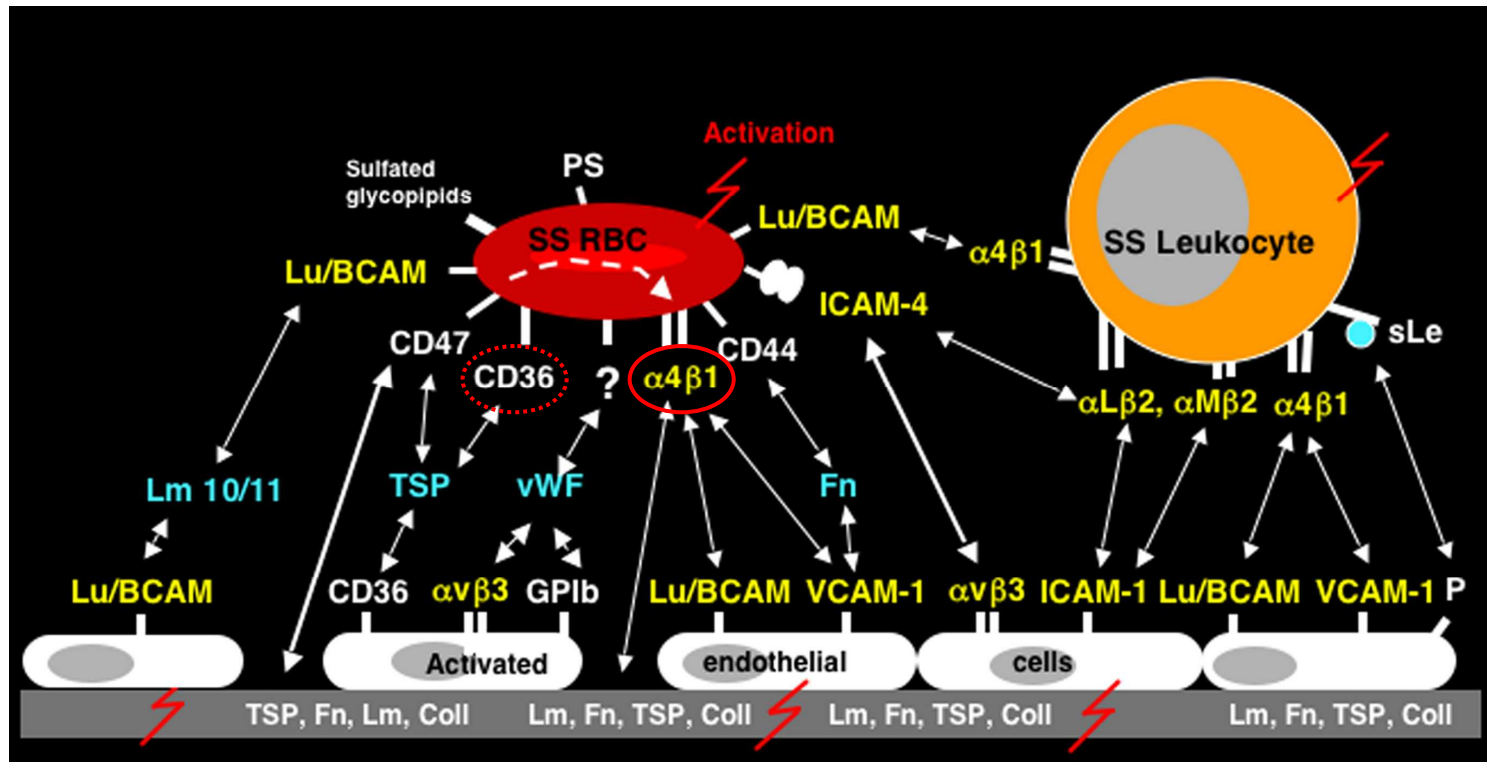
(Charache S et al, N Engl J Med 1995)

but

⇒ Early clinical response

⇒ Delayed and highly variable Hb F increase

Could HC affect cell adhesion?

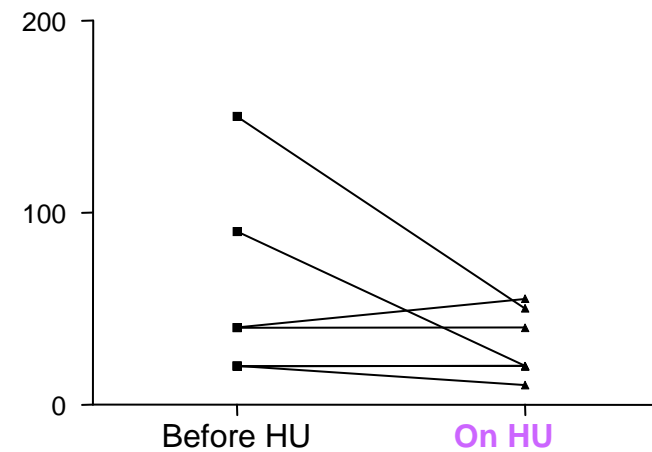
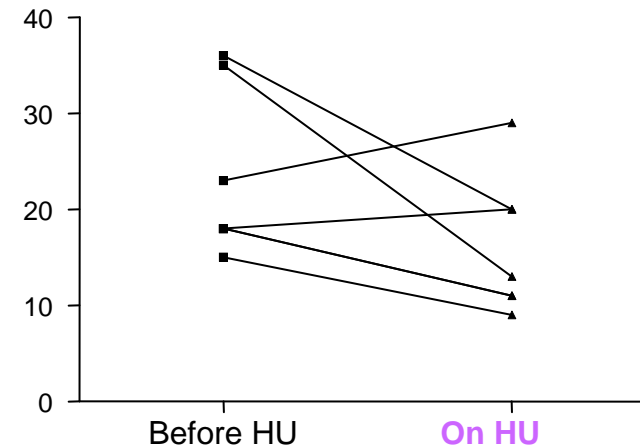
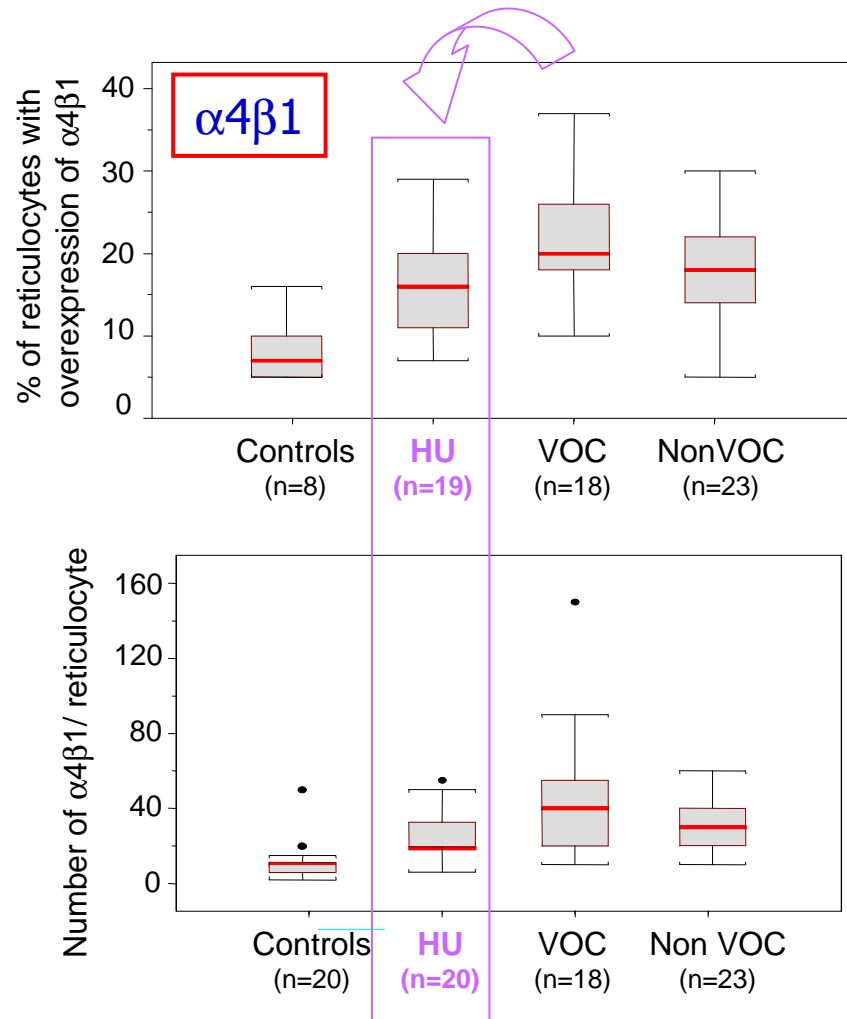


from JP Cartron

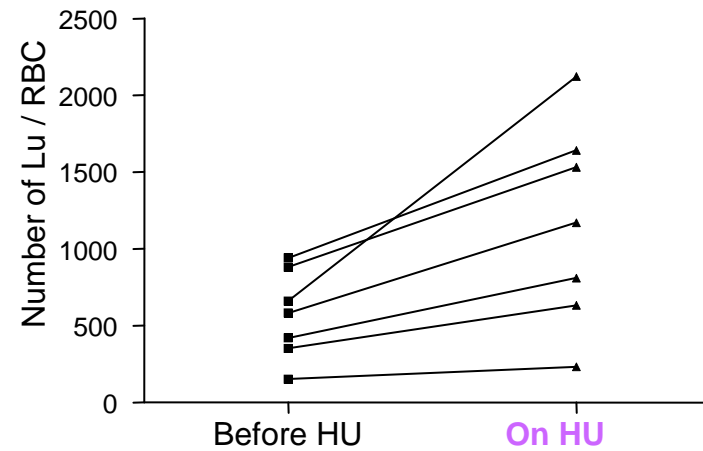
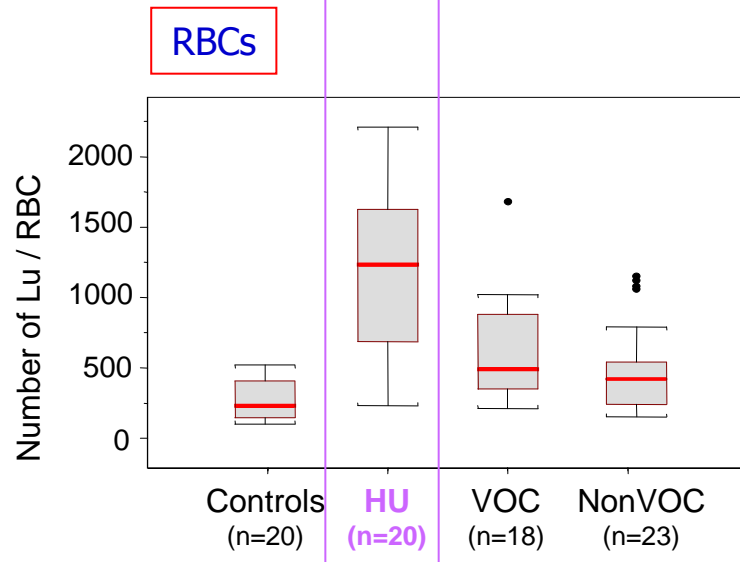
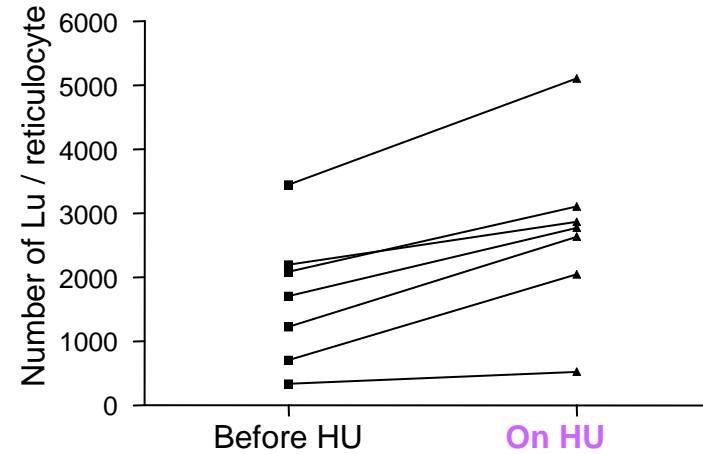
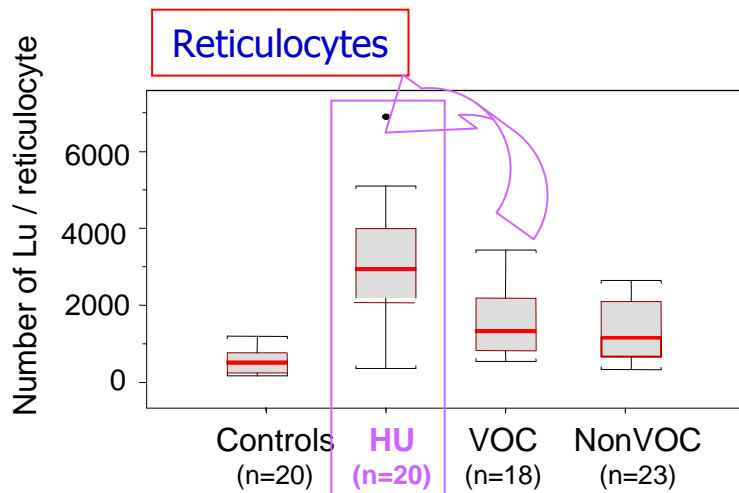
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- ⇒
- expression of adhesion molecules on RBCs?
 - endothelial cells?

in vivo, HC reduces the expression of the $\alpha 4\beta 1$ integrin (and CD36) on reticulocytes

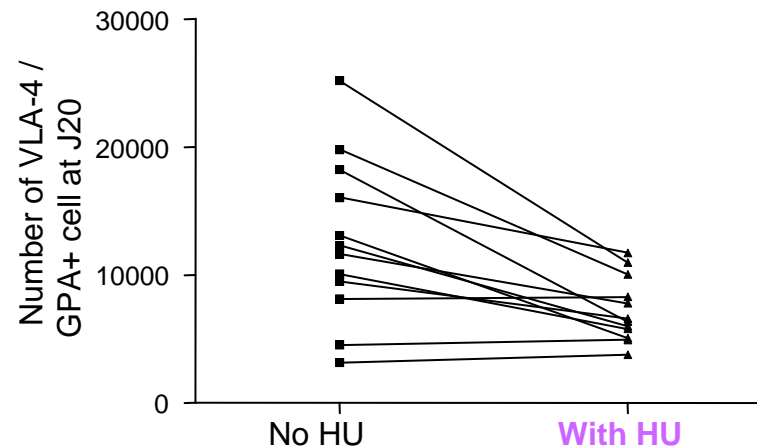


But paradoxically, *in vivo*, HC enhances the expression of BCAM/Lu

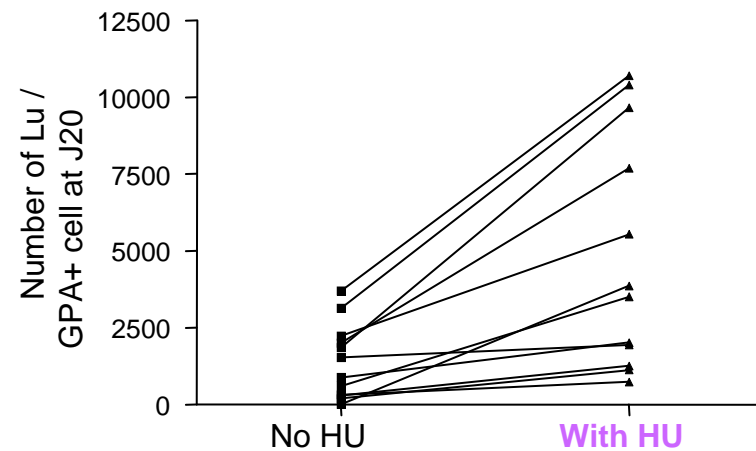


in vivo results are mimicked *in vitro* on erythroid progenitors in culture

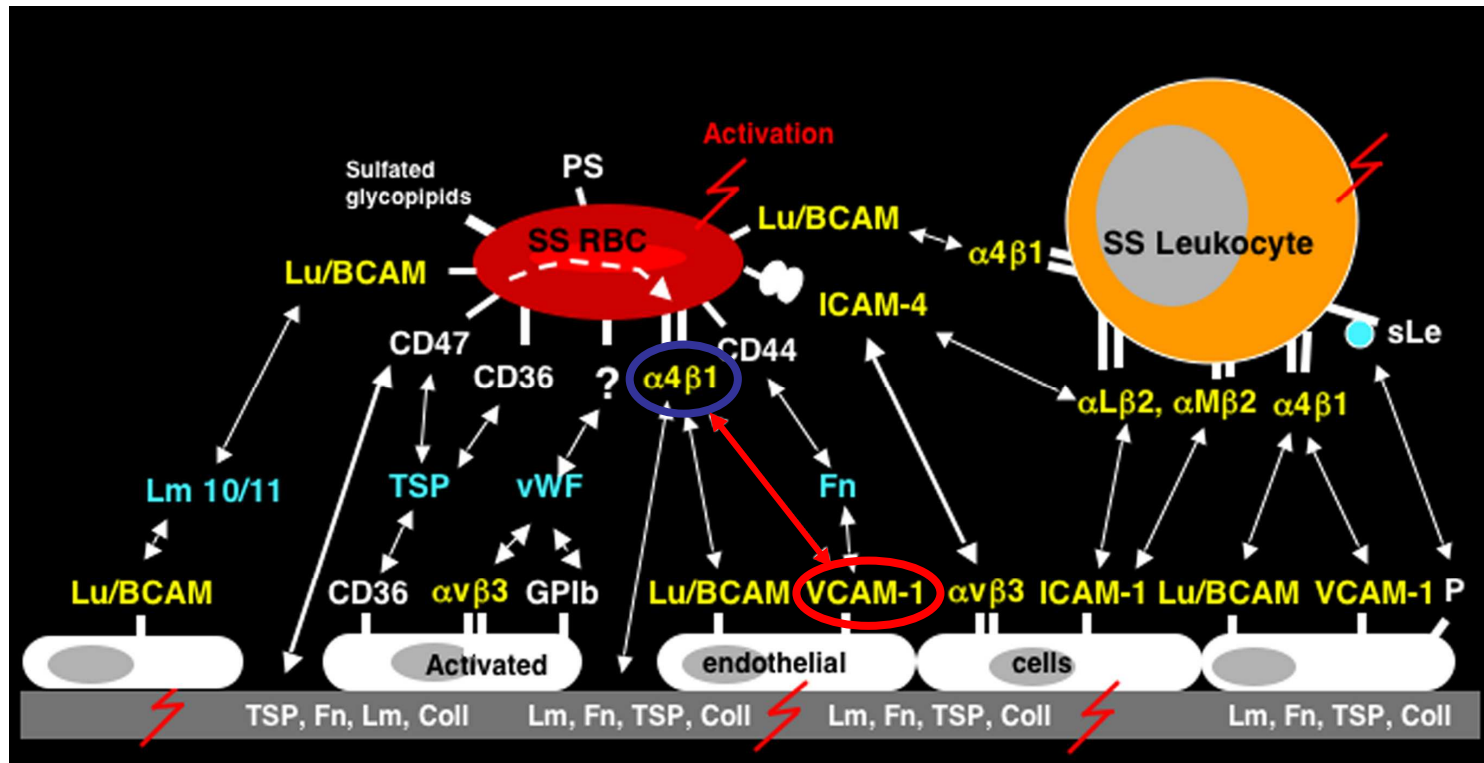
$\alpha 4\beta 1$ integrin
(VLA-4)



BCAM/Lu



Could HC affect cell adhesion?



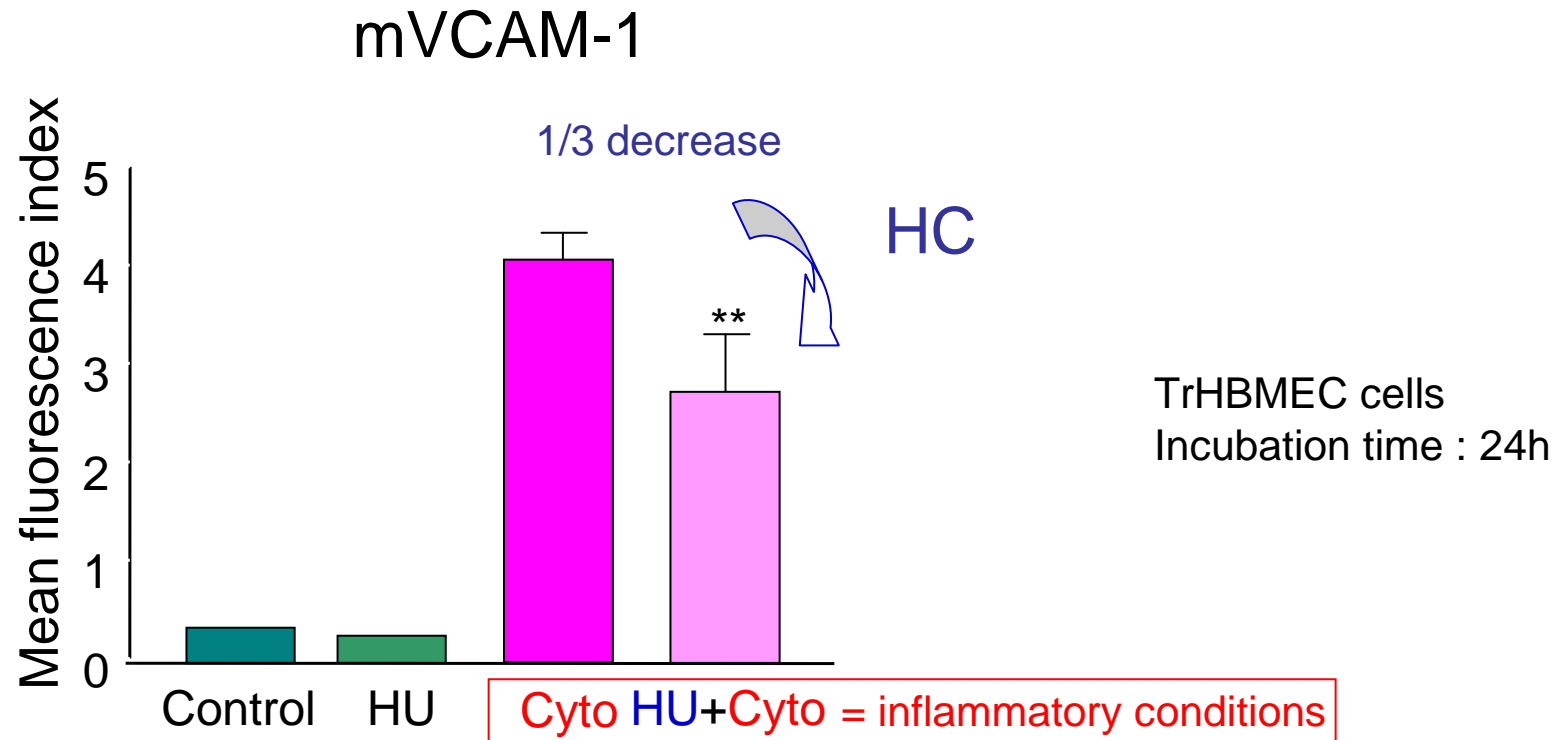
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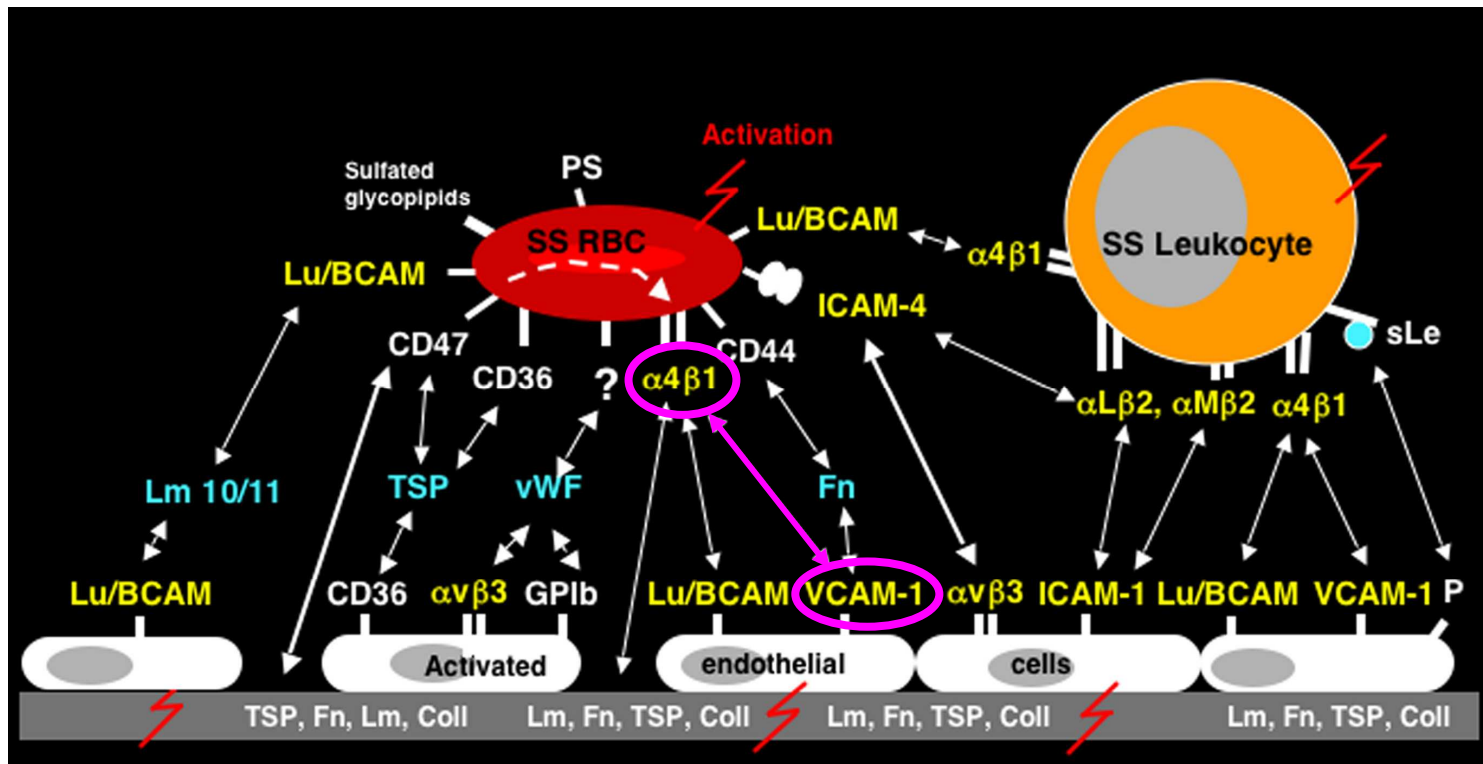
- expression of adhesion molecules on RBCs
 → endothelial cells?

Targeted approach:

HC decreases VCAM-1 expression at the surface of endothelial cells in culture (flow cytometry)



Could HC affect cell adhesion?

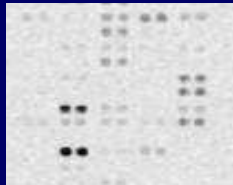


from JP Cartron

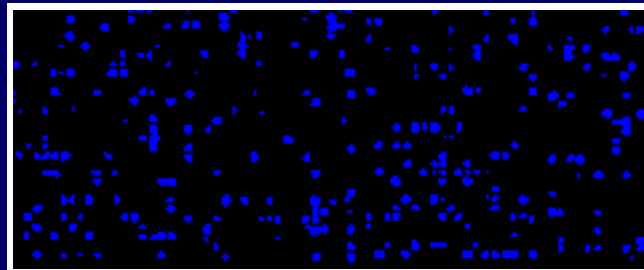
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- expression of adhesion molecules on RBCs
- ⇒ endothelial cells

Global approach: transcriptome analysis



405 cDNA
Immunology
hematology



30 000 genes
oligonucleotides

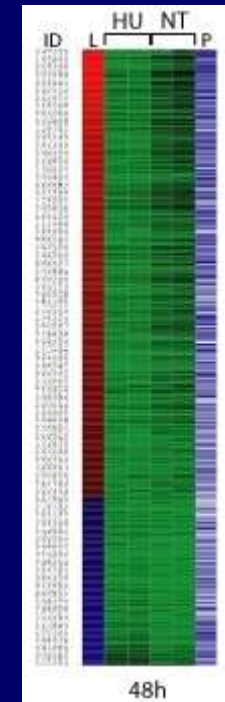
2,448 genes are modulated

confirms the previous data

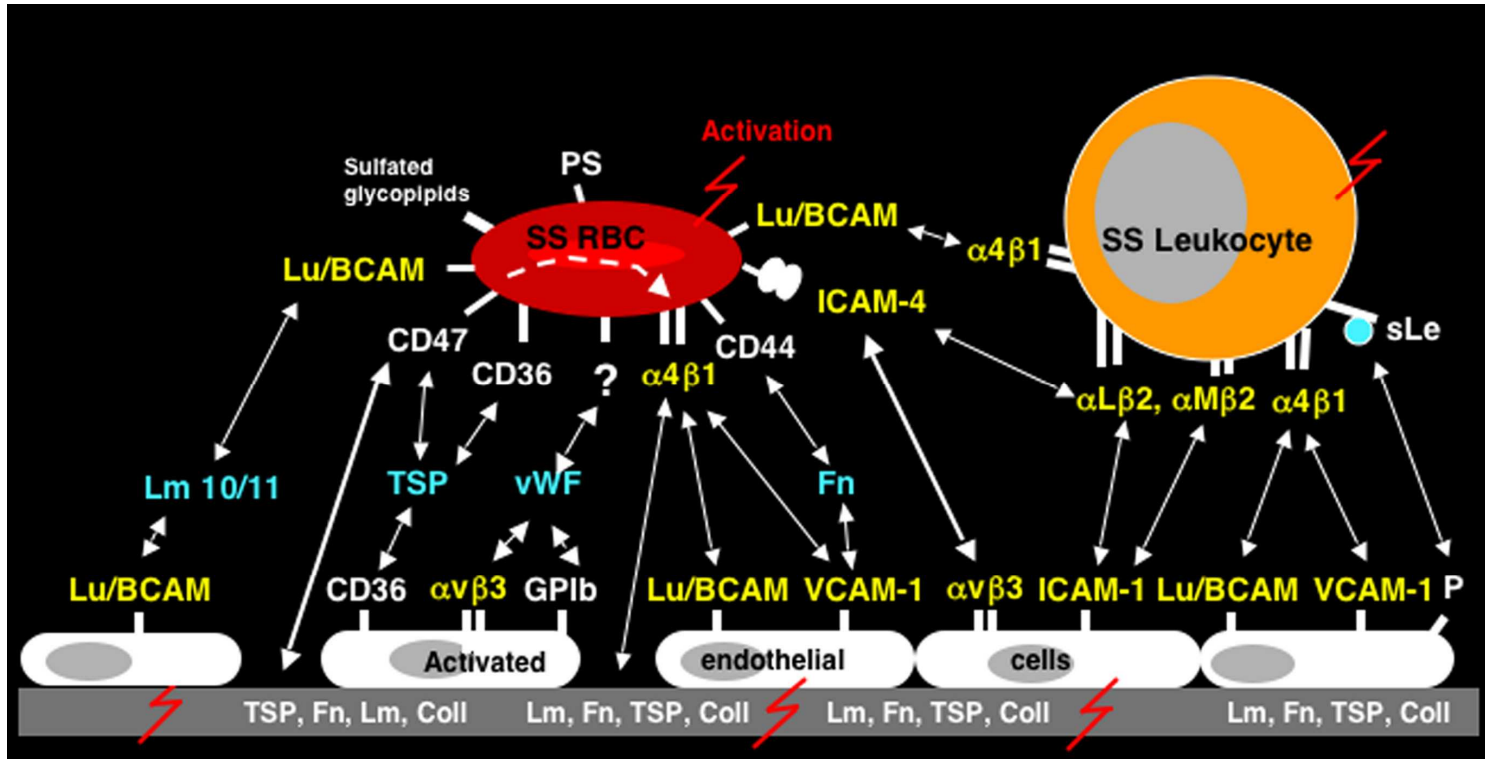
☞ Down-regulation: VCAM-1 (and also ET-1)

and extends them to other adhesion molecules

☞ Down-regulation: TSP-1, vWF, PECAM-1



Yes, HC can affect cell adhesion



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- expression of adhesion molecules on RBCs
- effect on endothelial cells

Conclusions

Cell adhesion to the endothelium is a major element for the initiation vasooclusion in SCD

Therapeutic target?

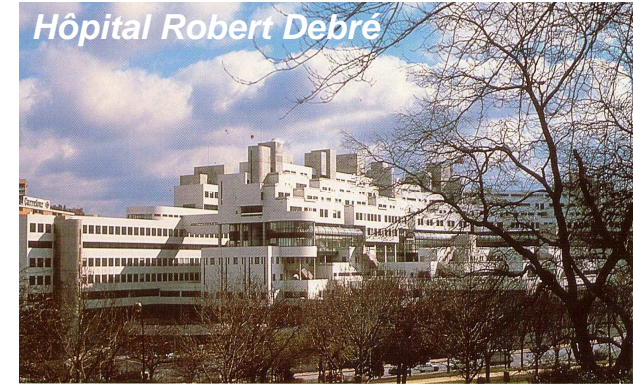
HC decreases cellular adhesion to endothelium

- *↘ proadhesive RBCs*
- *↘ adhesion properties of ECs*

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Physiopathology and Pharmacogenomics of
Therapeutics for Sickle Cell Disease