

VCAM1 modulation on endothelial cells

Implications for vasculopathy in sickle cell anemia

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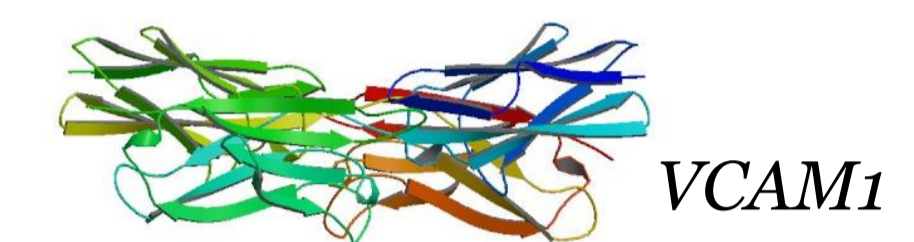


Background

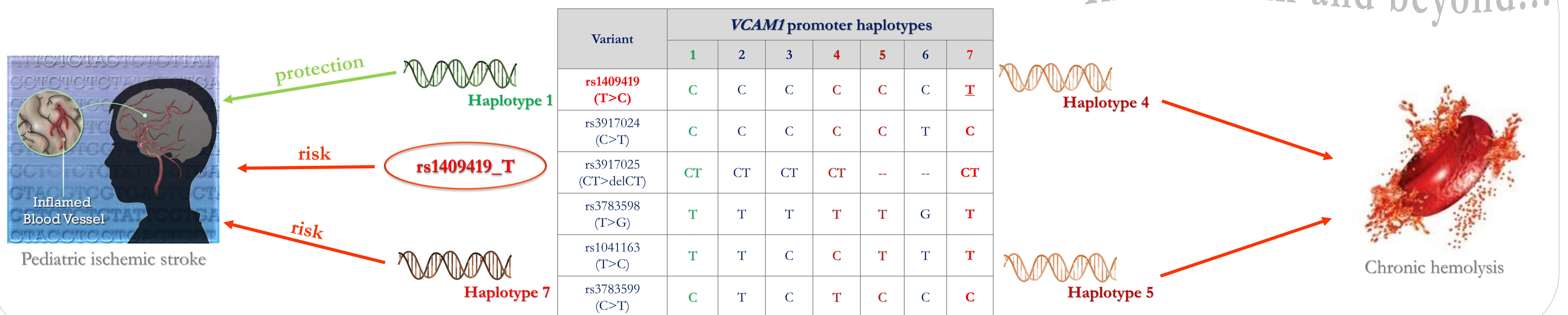
- Sickle cell anemia (SCA) – chronic vascular disease caused by homozygous c.20A>T mutation in the *HBB* gene, resulting in abnormal hemoglobin S (HbS) accumulation in erythrocytes;
- Pediatric subphenotypes include **cerebral vasculopathy (CVA)**, pain crisis, frequent infections and renal disease;
- Genetic modulation has been described to affect pathophysiology of SCA.

Research Question

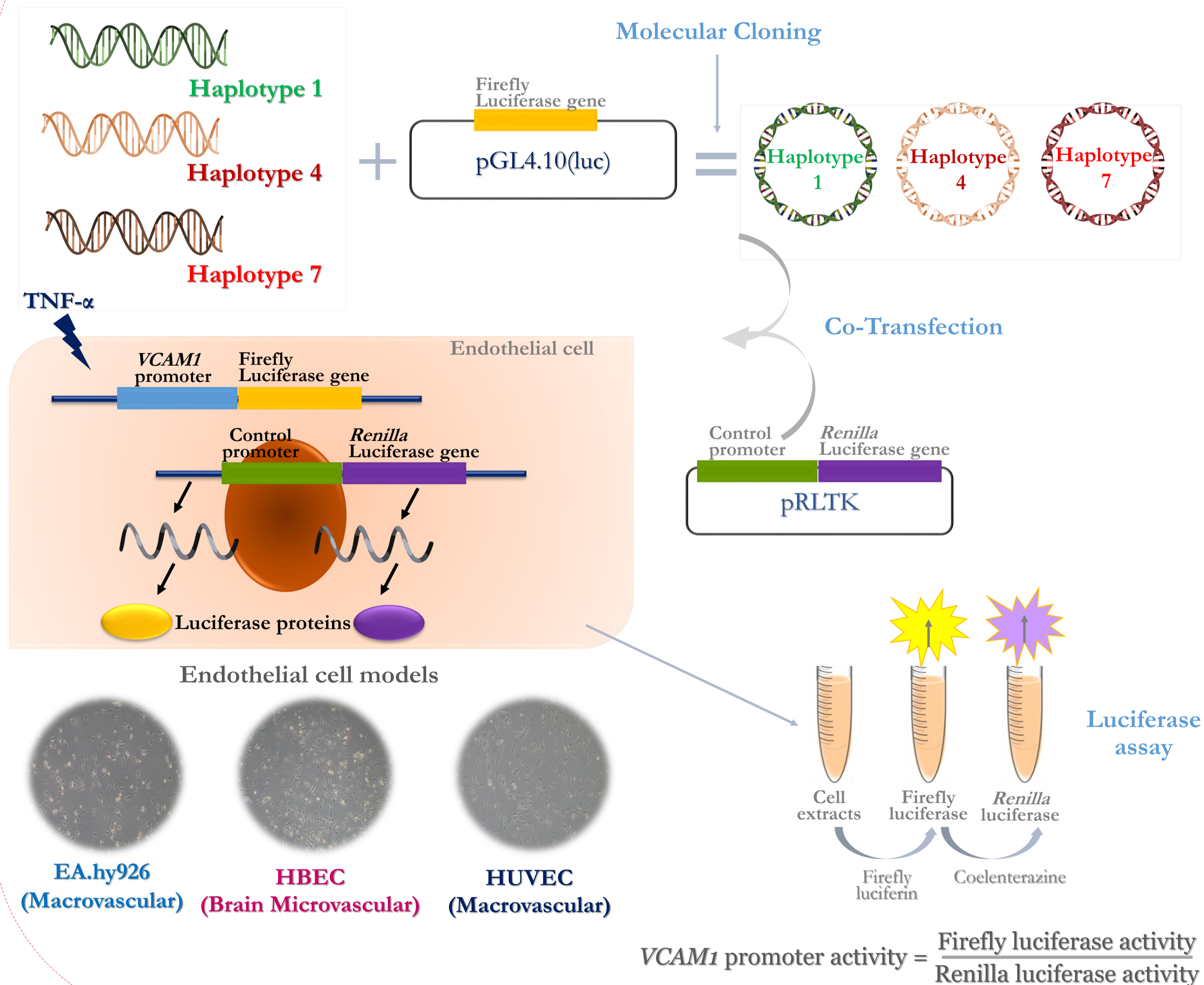
Could genes involved in endothelial cell adhesion, like VCAM1, act as modulators in the onset and severity of vasculopathy, namely pediatric CVA?



Previous Results



Experimental design



Recent Results

- Basal VCAM1 promoter activity is affected by all VCAM1 haplotypes tested, both in micro and macrovascular endothelial cells (Fig.1, left);
- Stimulation with TNF- α leads to a ≈ 2 -fold increase in promoter activity in cells transfected with haplotypes 4 or 7, when compared with non-stimulated cells;
- In a pro-inflammatory milieu, haplotype 1 leads to a less active VCAM1 promoter in brain microvascular cells, suggestive of a protective effect;
- The presence of haplotype 7 results the highest promoter activity, especially in brain microvascular cells (Fig. 1, right);
- The inductive effect of haplotype 4 is more significant in macrovascular cells, despite ≈ 2 -fold increase, in stimulated cells.

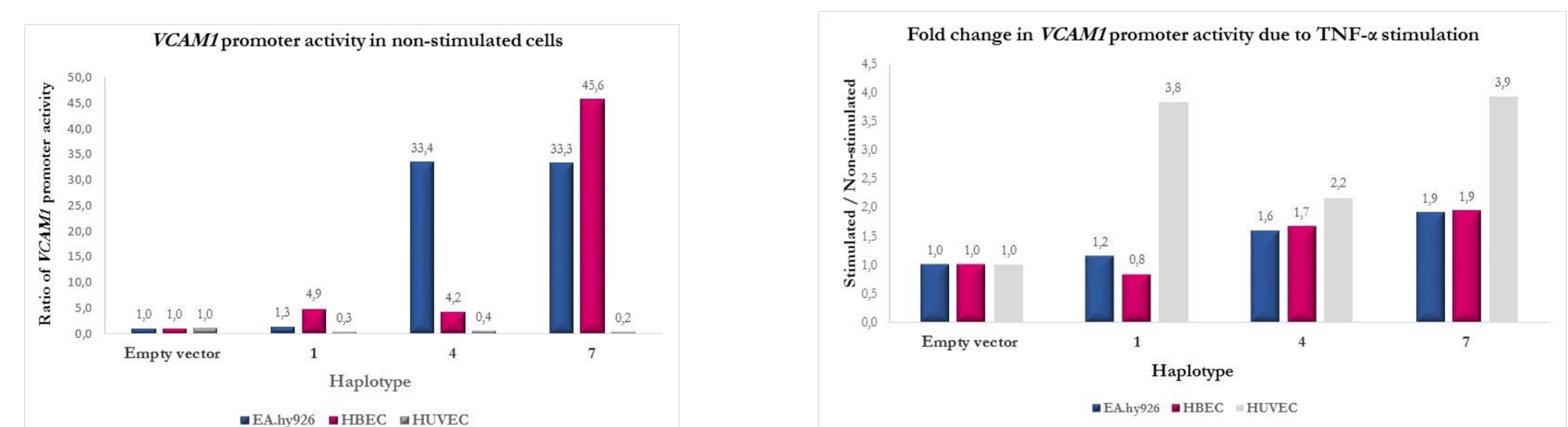


Figure 1. VCAM1 Promoter activity ratios, as measured by luciferase assay. normalised to empty vector construct; Left: Ratios in non-stimulated cells; Right: fold change of promoter activity in cells after TNF- α (8h, 20 ng/mL) stimulus when compared with non-stimulated cells.

Take home messages

- Functional studies show increased VCAM1 expression on cytokine-induced endothelial cells ;
- Promoter haplotypes, previously associated with CVA, show different effects and confirm VCAM1 modulation of endothelial cell response;
- The results on different endothelial cell models enhance the possibility of this effect extending beyond cerebral to systemic vasculopathy.

References

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