PhD Open Days

Genetic Modulation of Stroke in Children with Sickle Cell Anaemia

PhD Program in Biotechnology and Biosciences

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1. Subject

- Sickle cell anaemia (SCA) is an autosomal recessive genetic disease, caused by a mutation in the *HBB* gene, which results in the synthesis of an abnormal haemoglobin (HbS)
- HbS polymerises inside red blood cells causing them to be sickle-shaped, fragile, rigid and adherent-prone to vessel walls (endothelium) and to other blood cells
- Several pathways also play a role in disease severity such as endothelium dysfunction, cell adhesion, nitric oxide metabolism and haemolysis (Fig.1)
- SCA most catastrophic complication: cerebral vasculopathy (CVA), namely stroke and silent cerebral infarcts (SCIs)
- Current therapeutic approaches for CVA:
    - Transcranial Doppler, magnetic resonance imaging (MRI) or computerized tomography (CT scan) for risk assessment and diagnosis
    - Hydroxyurea and chronic blood transfusions
- Primary CVA prevention and prognosis are still not sensitive enough to detect all potentially affected children nor to evaluate long term prognosis

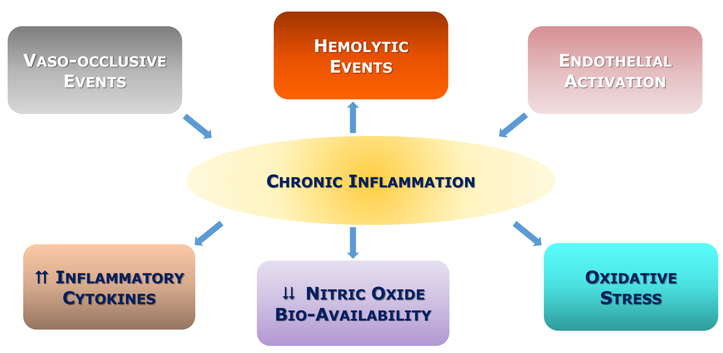

Fig. 1. Sickle cell anemia pathophysiology

2. Research Question(s)

- How do we design more effective approaches for paediatric CVA prevention in SCA?
- Could genetic variants act as modulators of CVA severity and, if so, could they be used as sensitive/specific biomarkers?

3. Plan of Action

Sample selection

- 70 SCA children (>= 3 years old)
- Several degrees of CVA (stroke, SCI, risk, normal)
- Database with clinical, imaging and laboratory data

Genotyping/ Sequencing

Candidate genes
- ***VCAM1*** (endothelial activation)
- ***ITGA4*** (cell-endothelium adhesion)
- ***NOS3*** (endothelial nitric oxide synthesis)

Association Studies

Statistic association
- **Stroke**, **SCIs**: *ITGA4*
- Stroke Risk: *VCAM1*
- Stroke or SCIs Protection: *NOS3*
- Haemolysis (markers): *VCAM1*, *ITGA4*

Gene Expression Studies

In Progress

- Endothelial cell models
- Changes in gene expression levels / altered regulation of gene expression

Pharmacological Studies

- Endothelial cell models
- Drug targets
- Differential response to drug treatment
- Drug tests: hydroxyurea, glutamine

Gene/Biomarker Panel

- Next generation sequencing panel
- Prognosis of disease severity

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