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

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