**Glycoprotein-VI: a stroke of luck in understanding thrombus formation**

Platelets are a group of anucleated cells which are vital in haemostasis and tissue repair. They become activated in response to tissue damage and form a thrombus that provides the protective barrier to stem excessive bleeding. Whilst a fundamental step in curtailing haemorrhage, thrombus formation can occur inappropriately, promoted by several cardiovascular disease states including atherosclerosis and atrial fibrillation. In these conditions, aberrant platelet activation is seen, which permits the amalgamation of large thrombi that can embolise to distant sites and obstruct the flow of blood to major organs such as the brain and heart, starving them of oxygen.

Stroke and myocardial infarction are just two conditions that arise as a result of ischaemia due to atypical thrombus formation. BHF-funded PhD student Dr Isuru Induruwa, in collaboration with Dr Stephanie Jung and Professor Richard Farndale from the Department of Biochemistry, are investigating the role of platelet receptor glycoprotein (GP) VI in stroke and thromboembolism.

During vascular injury, damaged endothelium exposes collagen, the mainstay structural component that provides scaffolding for a myriad of tissues. Circulating platelets bind to collagen which instigates their subsequent activation leading to thrombosis. The thrombus is later strengthened by fibrin, the end product of the coagulation cascade.

GPVI has been documented to bind to collagen through its active, dimeric form, which instigates the signalling needed to activate platelets and initiate thrombosis. What Dr Induruwa and colleagues discovered however, is that GPVI also binds to fibrin, through the same collagen binding dimeric form.

Using a flow adhesion assay, whereby human blood samples are perfused over glass slides coated in collagen and fibrin, he found that indeed, fluorescently-labelled platelets in the blood, bound significantly less to fibrin and formed significantly smaller thrombi when GPVI-dimer was inhibited using a GPVI-specific antibody.

This discovery is indeed promising and Dr Induruwa is now shifting his focus onto its potential clinical applications. Atrial fibrillation (AF) is one of the most common cardiac arrhythmias and is associated with thrombus formation and subsequent stroke. Along with Dr Elizabeth Warburton through their collaboration with Professor Willem Ouwehand in the Department of Haematology, Dr Induruwa is currently recruiting patients with atrial fibrillation to investigate their levels of GPVI on the platelet surface, as well their platelet response to collagen and fibrin.

These findings provide exciting insight into platelet biology and highlight GPVI as a potential target. Its therapeutic potential may not only be limited to stroke. “Large artery emboli such as in the coronary arteries are predominantly due to vessel damage and exposed collagen” Dr Induruwa explained. “Whilst thrombi cardio-embolic strokes as seen in AF are due to fibrin being the primary target for platelet activation”. The origin of the embolus is vital in providing targeted, efficacious treatment. The findings that Dr Induruwa and his colleagues demonstrate have showcased GPVI as a major culprit in thrombus formation, lending itself as an attractive candidate for pharmacological intervention.

Dr Induruwa explains: “This research suggests that GPVI-inhibition could avoid the dichotomy in the treatment of stroke between large artery stroke, treated with antiplatelets and cardioembolic stroke treated with anticoagulants”

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