Title:

Development of targeted CD39 as a therapy of stroke

Aim:

Stroke is caused by obstructed blood flow (ischaemia). Endothelial dysfunction largely underpins ischaemia pathogenesis, leading to aggravated inflammatory response and increased oxidative stress, culminating in thrombo-inflammatory response. Purinergic signaling is an endogenous molecular pathway, where CD39 and CD73 catabolize extracellular adenosine triphosphate (eATP) to adenosine. After ischemia, eATP is released, triggering thrombosis and inflammation. In contrast, adenosine is anti-thrombotic, protects against oxidative stress, and suppresses the immune response.

Our group developed a bifunctional compound - αVCAM-CD39 that targets dysregulated endothelium and promotes adenosine generation in site of infarct, localising antithrombotic and anti-inflammatory effects of CD39. The aim was to demonstrate that αVCAM-CD39 will improve stroke outcome in murine models of stroke (middle cerebral artery occlusion MCAo) when given as a single agent, will maximise the benefit of tPA in ischaemic stroke, as well as reduce tPA-related neurotoxicity.

Method:

Transient MCAo was utilised as model of stroke. Test drugs αVCAM-CD39 and controls were given 3h after 30min ischaemia. Assessments at 24h included neurological function, infarct volume, perfusion, albumin extravasation.

Results:

We showed that there was overall improvement in neurological deficit in treated mice after MCAo. MRI revealed treated mice had significantly smaller infarcts compared to saline and control treated mice. It was further found that blood flow in the brain was increased after drug treatment. There was less albumin extravasation in treated mice after MCAo, suggesting αVCAM-CD39 conferred neuroprotection in the brain through preservation of BBB permeability. We also found that our drug not only did not perturb haemostasis after tPA treatment, but also further mitigated tPA-related blood brain barrier permeability and infarct volume.

Conclusion:

αVCAM-CD39 is a novel therapeutic that can promote neuroprotection, reduce tissue damage and inflammation in the brain after stroke in mice. These findings suggest that αVCAM-CD39 could be a new avenue of stroke therapy and could potentially be used in other cerebrovascular diseases where endothelial dysfunction is a constant underlying pathology.