STEM CELL AND MOLECULAR INVESTIGATIONS FOLLOWING FOCAL CEREBRAL ISCHEMIA

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Published manuscript:

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Submitted manuscripts:

Preclinical studies on human cell-based therapy in rodent ischemic stroke models: where are we now after a decade? *Stem Cells*, 2012.

Npas4 upregulation in the corticolimbic network following focal cerebral ischemia. *European Journal of Neuroscience*, 2012.

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ABSTRACT

This thesis revolves around a general theme – cerebral ischemia. Stroke is the second leading cause of mortality after cardiovascular disease and the single primary cause of long-term adult disability worldwide. The number of stroke victims will only continue to rise due to the ageing population. Two out of three stroke patients survive the insult; however, neurological deficits which ensue are often debilitating and devastating. Chapter 1 presents a review of literature on the pathophysiology of ischemic stroke as well as on preclinical stroke research which underlies studies undertaken in this thesis.

Current ischemic stroke treatment regimens are not without their respective limitations, hence alternative, more effective, strategies are being developed to improve post-stroke functional recovery. One such approach is cell-based therapy involving the transplantation of exogenous stem/progenitor cells. Chapter 2 demonstrates the therapeutic efficacy of adult human dental pulp stem cells (DPSCs), a novel population of stem cells isolated from wisdom teeth, following intracerebral transplantation in a rodent model of focal cerebral ischemia. Significant improvement in forelimb sensorimotor function was observed at 4 weeks post-treatment, along with targeted migration of grafted cells toward the infarct area and minimal cell survival in the host brain. This suggests that human DPSCs are likely to mediate post-stroke neurobehavioral improvement via mechanisms other than endogenous neural cell replacement.

The onset of cerebral ischemia triggers a cascade of molecular events in the brain including the expression of early response transcription factors, one of which being the neuronal Per-Arnt-Sim domain protein 4 (Npas4). Although *Npas4* transcript levels have been reported to be robustly upregulated following an ischemic insult, little is known of its role in cerebral ischemia. Chapter 3 addresses this by characterizing the *in vivo* neuroanatomical expression profile of the Npas4 protein in a rat stroke model. Focal cerebral ischemia induced an early, transient and robust upregulation of Npas4 with a unique differential expression pattern in corticolimbic regions of the rodent brain which critically subserve cognitive and emotional functions, thus implying that Npas4 may play a role in post-stroke cognitive and emotional symptoms, prevalent stroke-associated neurological deficits with detrimental effects on functional recovery.

Previous studies have implicated Npas4 in the protection of neuronal cells against excitotoxic stimuli and apoptotic stress *per se* but not in the context of stroke. Chapter 4 further examines a possible role for Npas4 in neuroprotection following cerebral ischemia using a loss-of-function approach in an *in vitro* model of primary cultured cortical neurons subjected to oxygen and glucose deprivation (OGD). Knockdown of Npas4 expression led to decreased cell viability as well as increased neurite and dendrite fragmentation following an OGD insult. These findings are suggestive of the involvement of Npas4 in neuronal ischemic tolerance and the maintenance of neuronal network integrity after a stroke.