NEURAL STEM/PROGENITOR CELLS IN THE POST-ISCHEMIC ENVIRONMENT:
Proliferation, Differentiation and Neuroprotection

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Avhandlingen baseras på följande delarbeten:

I. Faijerson J., Tinsley R.B., Apricó K., Thorsell A., Nodin C., Nilsson M., Blomstrand F., and Eriksson P.S.
Reactive astrogliosis induces astrocytic differentiation of adult neural stem/progenitor cells *in vitro*. *Journal of Neuroscience Research* (2006) 84:1415-1424.

II. Faijerson J., Anderson M.F., Apricó K., Nilsson M., Eriksson P.S. and Komitova M.
Gene expression profiling in the perifocal neocortex after experimental stroke in rats: TRH up-regulation and effects on adult neural stem/progenitor cells. *In manuscript.*

III. Tinsley R.B.*, Faijerson J.* and Eriksson P.S.
Efficient non-viral transfection of adult neural stem/progenitor cells, without affecting viability, proliferation or differentiation. *Journal of Gene Medicine* (2006) 8:72-81.

IV. Faijerson J.*, Tinsley R.B.*, Thorsell A., Strandberg J., Hanse E., Sandberg M. and Eriksson P.S.
Adult neural stem/progenitor cells reduce excitotoxicity via pentinin, a novel neuroprotective peptide. *In manuscript.*

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Abstract
Stroke is one of the leading causes of chronic disability and death in the Western world. Today, no treatment can repair the cellular loss associated with an ischemic lesion. However, the discovery and dynamic regulation of neural stem/progenitor cells in the adult mammalian brain has resulted in exciting possibilities for future therapeutic interventions. Endogenous or grafted neural stem/progenitor cells are activated following an ischemic insult. These cells undergo directed migration towards infarcted areas, and differentiate in response to the insult. Unfortunately, the results of this regenerative effort are limited compared to the amount of tissue loss. This could be due to low survival of the recruited cells, but could also be explained by insufficient activation or dysfunctional lineage selection. Whether the lineage selection of neural stem/progenitor cells is altered following a lesion in the brain, what signals that are responsible for their activation or whether these cells can participate in post-lesion regeneration, astrogliosis or neuroprotection have yet to become clear. A greater understanding of these processes is necessary for finding ways to improve the endogenous regenerative capacity.
We found that reactive astrocytes, a prominent part of the post-ischemic environment, induced astroglial differentiation of adult neural stem/progenitor cells *in vitro*. Moreover, astrocytes derived from these cells were shown to participate in glial scar formation *in vitro*.
After studying gene expression in the peri-infarct region following focal ischemia, the expression of several genes was induced. We chose to focus our attention on one of these genes and its product, thyrotropin-releasing hormone (TRH). Immunoreactivity for TRH was found in several areas in both lesioned and intact brain regions, including in microglia present in the areas surrounding the lesion. Furthermore, TRH receptors were expressed on cultured neural stem/progenitor cells and TRH potently induced the proliferation of these cells. TRH is an interesting target for stroke treatment, but it also has many central effects in the brain and systemic administration may prove problematic. An interesting protocol for local delivery of TRH would be by grafting stem/progenitor cells, genetically engineered to secrete the peptide. In order to create a foundation for neuroprotective gene therapy, we developed efficient methods for non-viral transfection of neural stem/progenitor cells.
Since neural stem/progenitor cells migrate towards the ischemic area we wanted to investigate whether these cells secreted factors that could protect neurons against excitotoxicity, the main inducer of cell death following a stroke. Mass spectrometric analysis of factors secreted from cultured neural stem/progenitor cells led to the identification of a novel neuroprotective peptide, which we termed pentinin. This peptide potently reduced excitotoxicity in both mature and immature neurons in an *ex vivo* hippocampal slice model.
The results presented in this thesis show that the proliferation and differentiation of neural stem/progenitor cells can be dramatically affected by factors in the post-ischemic environment. Furthermore, the results suggest that neural stem/progenitor cells can participate in both glial scar formation and neuroprotection after an ischemic lesion. Finally, a novel neuroprotective peptide was identified. This peptide may be important for the protection of endogenous cells following insults in the brain and may represent an effective novel target for the treatment of stroke.

Keywords: Neural stem cells, neural progenitor cells, stroke, ischemia, reactive astrocytes, astrogliosis, proliferation, differentiation, neurogenesis, excitotoxicity, transfection, neuroprotection

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