THE ROLE OF ASTROCYTES IN STROKE, BRAIN PLASTICITY AND NEUROGENESIS

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin vid Göteborgs universitet kommer offentligen att försvaras i hörsal Karl Kylberg, Medicinaregatan 7, Göteborg, torsdagen den 30 maj 2013 kl. 13:00

av

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Avhandlingen baseras på följande delarbeten:

I. Li L, Lundkvist A, Andersson D, Wilhelmsson U, Nagai N, Pardo AC, Nodin C, Ståhlberg A, Aprico K, Larsson K, Yabe T, Moons L, Fotheringham A, Davies I, Carmeliet P, Schwartz JP, Pekna M, Kubista M, Blomstrand F, Maragakis N, Nilsson M, Pekny M.
Protective role of reactive astrocytes in brain ischemia.
J Cereb Blood Flow Metab. 2008 Mar;28(3):468-81.

II. Wilhelmsson U, Faiz M, de Pablo Y, Sjöqvist M, Andersson D, Widestrand A, Potokar M, Stenovec M, Smith PL, Shinjyo N, Pekny T, Zorec R, Ståhlberg A, Pekna M, Sahlgren C, Pekny M.
Astrocytes negatively regulate neurogenesis through the Jagged1-mediated Notch pathway.
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III. Ståhlberg A, Andersson D, Aurelius J, Faiz M, Pekna M, Kubista M, Pekny M.
Defining cell populations with single-cell gene expression profiling: correlations and identification of astrocyte subpopulations.
Nucleic Acids Res. 2011 Mar;39(4):e24.

IV. Andersson D, Wilhelmsson U, Nilsson M, Kubista M, Ståhlberg A, Pekna M, Pekny M.
Plasticity response in the contralesional hemisphere after subtle neurotrauma: gene expression profiling after partial deafferentation of the hippocampus.
Submitted

V. Andersson D, Wilhelmsson U, Möllerström E, de Pablo Y, Puschmann P, Nilsson M, Pekna M, Ståhlberg A, Pekny M.
Molecular definition of astrocytes in unchallenged and injured hippocampus, a single-cell gene expression study.
Manuscript

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ABSTRACT

Astrocytes, one of the most abundant and heterogeneous cell types in the central nervous system, fulfill many important roles in the healthy and injured brain. This thesis investigates the role of astrocytes in the neurogenic niche and the astrocyte response in stroke and neurotrauma. Using gene expression profiling on a global level as well as on a single-cell level and applying it to disease and transgenic models in vivo and in vitro, we have addressed molecular bases of these responses and molecular signatures of the subpopulations of astrocytes. Following injury, stroke or neurodegenerative diseases, astrocytes upregulate intermediate filament (nanofilament) proteins glial fibrillary acidic protein and vimentin along with many other genes, in a process referred to as reactive gliosis. Results presented in this thesis show that mice with attenuated reactive gliosis developed larger infarct volumes following experimental brain ischemia, compared to controls, implying that reactive gliosis is neuroprotective. Using astrocyte and neurosphere co-cultures, we show that astrocytes inhibit neuronal differentiation through cell-cell contact via the Notch signaling pathway and that intermediate filaments are involved in this process. We found that even a very limited focal trauma triggers a distinct brain plasticity response both in the injured and contralesional hemisphere and that this response at least partly depends on activation of astrocytes. Finally, using single-cell gene expression profiling in vitro and in vivo, we show that the astrocyte population is highly heterogeneous, we attempt to define astrocyte subpopulations in molecular terms, and we demonstrate that astrocyte subpopulations respond differentially to a subtle neurotrauma both in the injured and contralesional hemisphere.

Keywords: astrocytes, reactive gliosis, stroke, neurotrauma, brain plasticity, intermediate filaments, nanofilaments, GFAP, vimentin, neurogenesis, neural stem/progenitor cell, single-cell gene expression profiling

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