THE ROLE OF REACTIVE ASTROCYTES IN BRAIN ISCHEMIA AND NEUROTRAUMA

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Göteborgs universitet kommer att offentligen försvaras i hörsal ”Arvid Carlsson”, Medicinaregatan 3, Göteborg, fredagen den 15 december 2006 kl 09.00
av

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Avhandligen baseras på följande delarbeten:

I. Runfeng Jing, Ulrika Wilhelmsson, William Goodwill, Lizhen Li, Yihang Pan, Milos Pekny and Omar Skalli.
Synemin is Expressed in Reactive Astrocytes in Neurotrauma and Interacts Differentially with Vimentin and GFAP Intermediate Filament Networks.
Submitted

II. Lizhen Li, Andrea Lundkvist, Daniel Andersson, Ulrika Wilhelmsson, Nobuo Nagai, Andrea Pardo, Christina Nodin, Anders Ståhlberg, Karina Aprico, Kerstin Larsson, Takeshi Yabe, Lieve Moons, Andrew Fotheringham, Ioan Davies, Peter Carmeliet, Joan P. Schwartz, Marcela Pekna, Mikael Kubista, Fredrik Blomstrand, Nicholas Maragakis, Michael Nilsson and Milos Pekny.
Protective Role of Reactive Astrocytes in Brain Ischemia.
Manuscript

III. Maja Potokar, Marko Kreft, Lizhen Li, Daniel Andersson, Tina Pangršič, Helena H. Chowdhury, Milos Pekny and Robert Zorec.
Cytoskeleton and Vesicle Mobility in Astrocytes.
Traffic. In press

IV. Ulrika Wilhelmsson, Lizhen Li, Marcela Pekna, Claes-Henric Berthold, Sofia Blom, Camilla Eliasson, Oliver Renner, Eric Bushong, Mark Ellisman, Todd E. Morgan and Milos Pekny.
Absence of Glial Fibrillary Acidic Protein and Vimentin Prevents Hypertrophy of Astrocytic Processes and Improves Post-Traumatic Regeneration.
Journal of Neuroscience 24:5016-5021, 2004

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ABSTRACT

Astrocytes are the most abundant cell type in the central nervous system (CNS) and increasing evidence now suggests that they play an active role in various brain functions. Astrocytes are involved in the induction and maintenance of the blood brain barrier, as well as the induction and stabilization of neuronal synapses. Moreover, astrocytes control the extracellular ionic homeostasis, recycle neurotransmitters and are interconnected through gap junctions into a network. Astrocytes become reactive, a process known as reactive gliosis, in CNS pathologies, such as ischemia, neurotrauma or neurodegeneration. Major features of reactive gliosis include hypertrophy of astrocyte processes, upregulation of glial fibrillary acidic protein (GFAP) and vimentin and re-expression of nestin. GFAP, vimentin and nestin are constituents of intermediate filaments (IFs), which are part of the cytoskeleton. It remains largely unclear whether reactive astrocytes are beneficial or detrimental in CNS pathologies. In this thesis, the role of reactive astrocytes was studied in brain ischemia and neurotrauma by using a mouse model in which the *GFAP* and *vimentin* genes were ablated. These *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice are devoid of astrocyte IFs and show attenuated reactive gliosis following CNS injury. We found that, after neurotrauma, reactive astrocytes produce synemin, another IF protein, and that synemin needs vimentin to form IFs. We propose that synemin expression is part of the response of astrocytes to neurotrauma and thus, synemin might be a useful marker of reactive astrocytes. When subjected to brain ischemia, *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice have larger infarct volume than wildtype controls, which suggests that reactive astrocytes are protective in brain ischemia and limit the extent of the infarct. The absence of IFs affects vesicle trafficking in astrocytes. *GFAP*$^{-/-}$*Vim*$^{-/-}$ astrocytes have a decreased number of vesicles displaying directional mobility and fewer vesicles that travel for a long distance compared to wildtype astrocytes. This suggests that IFs may act as a structure supporting highly mobile vesicles in astrocytes. At an early stage after neurotrauma, *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice show a greater loss of synapses compared to wildtype. At a later stage, however, *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice show highly improved synaptic regeneration compared to wildtype controls. Thus, reactive astrocytes seem to be protective at an early stage after neurotrauma but inhibit regeneration later on.

Keywords: astrocytes, intermediate filaments, GFAP, vimentin, reactive gliosis, brain ischemia, neurotrauma

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