

THE EFFECT OF ASTROCYTES AND REACTIVE GLIOSIS ON NEUROGENESIS AND ASTROGENESIS IN MICE

AKADEMISK AVHANDLING

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av

Åsa Widestrand

Fakultetsopponent:
Professor Zaal Kokaia
Lund Stem Cell Center, Lunds universitet, Lund, Sverige

Avhandlingen baseras på följande delarbeten:

- I** Increased cell proliferation and neurogenesis in the hippocampal dentate gyrus of old *GFAP^{-/-}Vim^{-/-}* mice
Åsa Larsson, Ulrika Wilhelmsson, Marcela Pekna and Milos Pekny
Neurochemical Research, 2004 Nov; 29(11): 2069-73.

- II** Increased neurogenesis and astrogenesis from neural progenitor cells grafted in the hippocampus of *GFAP^{-/-}Vim^{-/-}* mice
Åsa Widestrand, Jonas Fajjerson, Ulrika Wilhelmsson, Peter L. P. Smith, Lizhen Li, Carina Sihlbom, Peter S. Eriksson and Milos Pekny
Stem Cells, 2007 Oct; 25(10): 2619-27

- III** GFAP and vimentin are negative regulators of the hippocampal neurogenic niche
Maryam Faiz*, Åsa Widestrand*, Ulrika Wilhelmsson, Sofia Linde, Peter L. P. Smith, Daniel Andersson, Helena Christianson, Barbora Slaba, Tulen Pekny, Marcela Pekna and Milos Pekny
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*this work represented a joint effort of the first two authors



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Åsa Widestrand

Department of Clinical Neuroscience and Rehabilitation, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Sweden

Abstract

Astrocytes are the most common cell type in mammalian central nervous system (CNS). Glial fibrillary acidic protein (GFAP) and vimentin constitute intermediate filaments (known also as nanofilaments), a part of the cytoskeleton, in astrocytes. In damaged CNS, astrocytes become reactive and increase the expression of GFAP and vimentin and alter the expression of the host of other genes, a process referred to as reactive gliosis. Reactive astrocytes have a neuroprotective effect in neurotrauma or brain ischemia, but they have also been shown to inhibit CNS regeneration. *GFAP^{-/-}Vim^{-/-}* mice are deficient in astrocyte intermediate filaments and after neurotrauma or in brain ischemia show less prominent reactive gliosis than wildtype mice.

Mild reactive gliosis occurs in the hippocampus of healthy aging individuals, both in rodents and humans. Neurogenesis in the dentate gyrus of the hippocampus is known to decline during life. We assessed the effect of age-related reactive gliosis on hippocampal neurogenesis in *GFAP^{-/-}Vim^{-/-}* and wildtype mice (Paper I). We found that attenuated reactive gliosis in aged *GFAP^{-/-}Vim^{-/-}* mice was linked to higher hippocampal cell proliferation and neurogenesis. Our data suggest that age-related reactive gliosis may be a cause for declining neurogenesis in aging brain.

Our research group previously showed that the attenuation of reactive gliosis in *GFAP^{-/-}Vim^{-/-}* mice improved integration of neural grafts. Here, we addressed whether *GFAP^{-/-}Vim^{-/-}* astrocytes affect neural progenitor cell differentiation in vitro and survival and differentiation of grafted neural progenitor cells in a neurogenic niche in the brain (Paper II). Using cocultures of neural progenitor cells and astrocytes, we found that *GFAP^{-/-}Vim^{-/-}* astrocytes increased the number of neural progenitor-derived neurons and astrocytes. When adult hippocampal progenitor cells were grafted in the hippocampal region, *GFAP^{-/-}Vim^{-/-}* recipients showed more graft-derived astrogenesis and neurogenesis. These findings suggest that attenuation of reactive gliosis may be a suitable strategy for enhancing adult neurogenesis and for increasing the efficiency of neural progenitor cell transplantation.

In the next study (Paper III), we found that the baseline and posttraumatic hippocampal neurogenesis and some aspects of learning and memory were improved in *GFAP^{-/-}Vim^{-/-}* mice compared to wildtype controls. Moreover, we provide evidence that astrocytes constitute an important niche for production of new neural cells in the adult hippocampus.

Key words: astrocytes, intermediate filaments, neural stem cells, neurogenesis, astrogenesis, hippocampus