FROM MICE TO MEN - ASTROCYTES AND NEURAL PROGENITOR CELLS IN NEURAL PLASTICITY AND REGENERATION

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Åke Göransson, Medicinaregatan 11, tisdagen den 28 februari 2017, kl.9.00

av **Meng Chen**

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Avhandlingen baseras på följande delarbeten

I. **Chen M**, Puschmann TB, Wilhelmsson U, Örndal C, Pekna M, Malmgren K, et al.: Neural progenitor cells in cerebral cortex of epilepsy patients do not originate from astrocytes expressing GLAST.
Cereb Cortex. 2016 Dec 14.

II. Möllerström E, Rydenhag B, Andersson D, Lebkuechner I, Puschmann TB, **Chen M**, et al.: Classification of subpopulations of cells within human primary brain tumors by single cell gene expression profiling.
Neurochem Res. 2015 Feb;40(2):336-52.

III. Chen M, Puschmann T, Marasek P, Inagaki M, Pekna M, Wilhelmsson U, et al: Increased neuronal differentiation of neurosphere cells derived from phosphovimentin-deficient mice.
Manuscript.

IV. de Pablo Y, **Chen M**, Möllerström E, Pekna M, Pekny M: Drugs targeting intermediate filaments can improve neurosupportive properties of astrocytes.
Submitted manuscript.

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Astrocytes, a key homeostatic cell type in the mammalian central nervous system (CNS), have various functions in health and diseases. In neurotrauma, stroke, epilepsy or neurodegenerative diseases, astrocytes become reactive, which is known as reactive gliosis. Two characteristic hallmarks of reactive gliosis are hypertrophy of astrocyte processes and up-regulation of the intermediate filament (also known as nanofilament) proteins GFAP, vimentin, nestin and synemin. Reactive astrocytes have a neuroprotective role in the acute stage of CNS pathologies, by handling the acute stress, limiting the tissue damage and restoring the homeostasis of the CNS, but persisting reactive gliosis in some situations can become maladaptive and lead to the inhibition of neural plasticity and other regenerative responses. Animal studies suggested that some reactive astrocytes can act as neural stem cells after injury.

We hypothesized that some reactive astrocytes within the epileptic foci of patients with epilepsy have neural progenitor cell properties. We studied material from surgical resections from patients with pharmacologically intractable epilepsy after we first established protocols for dissociating such tissue into single live cells. We showed that cells with neural progenitor cell properties exist in the epileptic cortex outside the well-established adult neurogenic regions (i.e. outside the subventricular zone and the hippocampal dentate gyrus), and demonstrated that these neural progenitor cells are not glutamate aspartate transporter (GLAST) expressing astrocytes.

Modulation of the astrocyte nanofilament system was proposed as a potential therapeutic strategy in some CNS pathologies. To assess the role of vimentin phosphorylation in neurogenesis, we used *VIM*$^{SA/SA}$ mice, in which the serine sites in the vimentin molecule that are phosphorylated during mitosis had been mutated, which show cytokinetic failure in fibroblasts and lens epithelial cells. We found that mutation of the serine sites phosphorylated in vimentin during mitosis leads to increased neuronal differentiation of neural progenitor cells, and suggest that this is a neural progenitor cell intrinsic phenotype.

We studied three drug candidates that could potentially decrease the expression of GFAP and the other astrocyte nanofilament proteins, and assessed their effect on neurosupportive properties and resilience of astrocytes to oxygen and glucose deprivation (OGD), an in vitro model for brain ischemia. We found that two of them increased survival of neurons co-cultured with astrocytes, which makes them potential candidates for attenuation of reactive gliosis in vivo.

Key words: astrocytes, intermediate filaments, reactive gliosis, GFAP, GLAST, vimentin, neural progenitor cells, neurogenesis, Bioactive3D culture system

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