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In vivo responses of neural progenitor cells to extracellular matrix signaling under pathological conditions

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i föreläsningsal Gösta Sandels, Medicinaregatan 9, den 12 juni, klockan 13.00

av

Reza Motalleb Zadeh

Fakultetsopponent:

Francis Szele, Professor

Department of Physiology, Anatomy and Genetics, University of Oxford, UK

Avhandlingen baseras på följande delarbeten

I. Motalleb R, Berns EJ, Patel P, Gold J, Stupp SI, Kuhn HG. In vivo migration of endogenous brain progenitor cells guided by an injectable peptide amphiphile biomaterial.
J Tissue Eng and Reg Med 2018; 12: e2123-e2133.

II. Motalleb R, Berns EJ, Stupp SI, Kuhn HG. Glial Response to an injectable peptide amphiphile biomaterial. *Manuscript*

III. Motalleb R, Lindwall C, Kuhn HG. Neurogenesis after cortical stroke in the adult brain of hyaluronan receptor RHAMM knockout mice. *Manuscript*

SAHLGRENSKA AKADEMIN

INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

GÖTEBORGS UNIVERSITET

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In vivo responses of neural progenitor cells to extracellular matrix signaling under pathological conditions

Reza Motalleb Zadeh

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

Abstract

The adult brain has an inherently low capacity for tissue regeneration, and neurons lost to disease or injuries are normally not replaced. This becomes especially apparent when stroke or brain trauma occurs. The discovery of neurogenesis and neural stem cells in the adult brain has opened up new avenues for treatment of the injured brain. In the adult brain, neural stem cells are present in two distinct neurogenic areas, the subventricular zone and the hippocampus. These neural stem cells are capable of generating new neurons throughout life. As these cells have been shown to respond to signals from the surrounding extracellular matrix, we were interested in how we can utilize these for the purpose of regenerating lost neurons. In **paper I**, we use an injectable self-assembling peptide amphiphile coupled to a migration-inducing peptide sequence derived from Tenascin-C, a glycoprotein natural occurring in the extracellular matrix of the neurogenic areas. In this paper, we re-directed cells from their normal path, the rostral migratory stream, to migrate into the cortex using the Ten-C-peptide amphiphile. Furthermore, this was done without causing an exacerbated glial response or glial scar. In **paper II** we used a similar biomaterial with another naturally occurring sequence, RGDS, derived from fibronectin. In this study, we were interested in the potential of the RGDS-peptide amphiphile as a possible cell scaffold for neural stem cell transplants. The introduction of a foreign material into the CNS can lead to a strong reactive gliosis response from endogenous astrocytes and microglia. Surprisingly, not only did the RGDS-peptide amphiphile not elicit a stronger glial response than the control needle wound injury, but it rather suppressed the reactivity of astrocytes and microglia. These results indicate great potential of the biomaterial for future use an artificial ECM for cell transplants in the CNS. In **paper III,** we were interested in the role of RHAMM, the receptor for hyaluronan, one of the most abundantly expressed glycosaminoglycans in the brain extracellular matrix, in stroke-induced neurogenesis. We observed RHAMM in both unlesioned and unlesioned animals being important for cell proliferation and neurogenesis in both the SVZ and hippocampus of the adult brain.

Keywords: Peptide Amphiphiles, Biomaterial, Tenascin-C, RGDS, RHAMM, Reactive Gliosis, Rostral Migratory Stream, Extracellular Matrix

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