SPP 1757

Modulation of glial diversity and functional heterogeneity concerning brain activity by the lipoprotein receptor-related protein 1 (LRP1) receptor and the glycoprotein of the extracellular matrix tenascin-C

Speaker:

Professor Dr. Andreas Faissner
Ruhr-Universität Bochum
Fakultät für Biologie und Biotechnologie
Lehrstuhl für Zellmorphologie und Molekulare Neurobiologie

Funding period:

from 2014 to 2020

Project description:

During the first funding period the laboratory has shown that the complex 487LeX and 5750LeX glycans of the LewisX (LeX) family are differentially expressed on the surface of radial glia stem and glial progenitor cells and permit the enrichment of glial subpopulations. The glycoprotein of the extracellular matrix tenascin C (Tnc) and the lipoprotein receptor related protein 1 (LRP1) were identified as carrier proteins. Tnc is a constituent of the stem cell niche matrisome and regulates the maturation of astrocyte progenitors. Applying digital time lapse video microscopy we could show that Tnc modulates the lineage trees and the cell cycle of embryonic spinal cord glial stem and progenitor cells. Preliminary data suggest the adult behave differently than the embryonic glial stem and progenitor cells. The functional heterogeneity of the micro milieu of neural stem cells will be addressed during the second funding period with reference to Tnc. LRP1 is a multifunctional receptor with multiple ligands, including particular components of the ECM. We could show that the deletion of LRP1 from glial stem and progenitor cells impairs neurogenesis and the generation of oligodendrocytes, and favours the differentiation of astrocytes. This effect relies partly on LRP1 dependent signal transduction, rather than on endocytosis. Selective deletion of LRP1 from cortical radial resulted in a severe neurological phenotype. Beginning with the third postnatal week increasing neuronal excitability and epileptic seizures leading to increased mortality were detected. Based on these results and preliminary data, we plan to investigate glial heterogeneity and its impact on neural activity on a mechanistic basis. The following aims will be addressed: i) the heterogeneity of embryonic and adult glial stem and progenitor cells will be explored with regard to their differential response to Tnc containing microenvironments using digital time lapse video microscopy; ii) the expression of the 487LeX and 5750LeX glycans in the adult CNS will be monitored and corresponding glial populations will be characterized; iii) the functional relevance of LRP1 in astroglial subpopulations with respect to overall CNS activity will be examined by conditional deletion in the GLASTCre/wtLRP1fl/flReporterfl/fl mouse model; iv) the functional significance of LRP1 in NG2 cell subpopulations with respect to overall CNS activity will be analysed by conditional deletion in the NG2Cre/wtLRP1fl/flReporterfl/fl mouse model. The project combines genetic, cell biological and biochemical approaches to examine the generation of glial heterogeneity and its influence on overall brain activity in a developmental perspective.

Quelle:
https://gepris.dfg.de/gepris/projekt/254968232?language=en