SPP 1757

Function and mechanisms specifying the heterogeneity of forebrain astrocytes

Speaker:

Professorin Dr. Magdalena Götz
Ludwig-Maximilians-Universität München
Biomedizinisches Centrum München
Physiologische Genomik

Funding period:

since 2014

Project description:

In the previous funding period we identified intriguing differences between parenchymal astrocytes from the cerebral cortex grey matter and the diencephalon. Most importantly we showed that diencephalic astrocytes proliferate in vivo and have neural stem cell hallmarks in vitro as they form multipotent and self-renewing neurospheres. Thus we have identified a novel neural stem cell niche in the adult brain and propose a novel concept of region-specific astrocytogenesis in vivo. In addition we identified a key regulator of these region-specific hallmarks of diencephalic astrocytes, Smad4. Inducible Smad4 deletion in astrocytes shows a selective reduction in astrocyte number in the diencephalon, but not the cerebral cortex, as well as a severe reduction in the neurosphere forming capacity of diencephalic astrocytes. In the first part of the project proposed for the coming funding period we would like to examine and understand the role of the ongoing astrocytogenesis in the adult diencephalon. This will be done by clonal analysis to determine the extent of astrocyte addition or turnover, as well electrophysiological recordings of proliferating astrocytes in the diencephalon to determine their functional properties and potential influences on the network properties. We will also perform behavior analysis of the Smad4 mutant mice as an entry point to understand the effects of reduced astrocytogenesis in the diencephalon. In the second part of the project we aim to understand to which extent the region-specific differences of diencephalic and cortical astrocytes depend on their location, i.e. extrinsic factors, or are intrinsically determined. Towards this end, we will transplant astrocytes from the cerebral cortex into the diencephalon to determine if the diencephalon environment is sufficient to elicit proliferation and neurosphere formation in astrocytes from the cerebral cortex. As Smad4 is a mediator of extrinsic or intrinsic mechanisms specifying diencephalic astrocyte hallmarks, we aim to identify its transcriptional targets that mediate these hallmarks of diencephalic astrocytes by RNA-seq and ChIP seq. Lastly we aim to examine WM astrocytes in comparison to diencephalic astrocytes, as recent RNA-seq data show that they also express proliferative genes and indeed first experiments show their proliferation and neurosphere formation. We now aim to determine if these properties of WM astrocytes are determined by the same of different mechanisms acting in the diencephalon. Taken together, these approaches allow tackling the novel concept of region-specific astrocytogenesis in the adult murine brain.

Quelle:
https://gepris.dfg.de/gepris/projekt/254847613?language=en