How are astrocytes made? Transcriptional regulation of astrocyte specification across development and adulthood.

Supervisory team:
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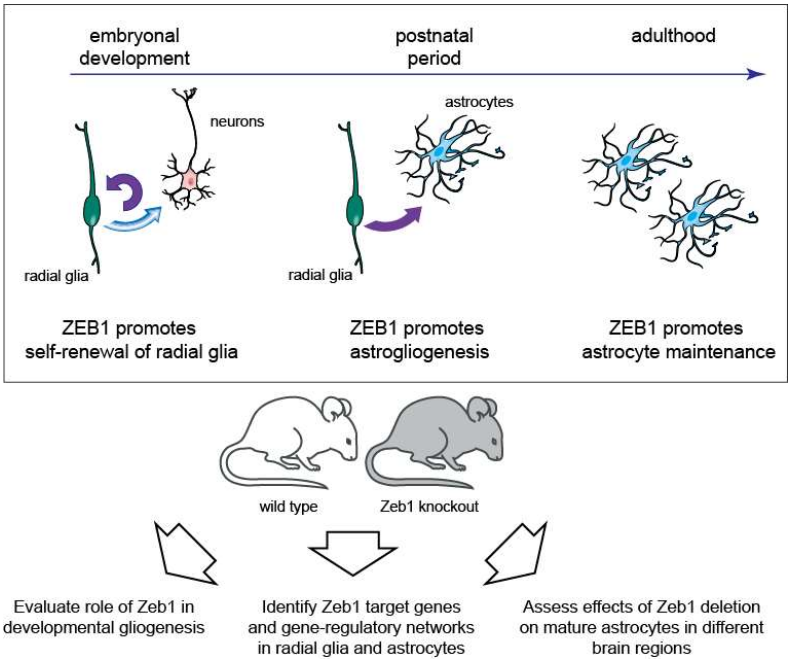
Project description:



The importance of glial cells (the non-excitable component of the nervous system) for proper brain function and homeostasis is being increasingly recognized, but our understanding of the factors that regulate their production and survival is still incomplete. This project will use interdisciplinary approaches to investigate the role of Zeb1 in the generation and maintenance of glial cells in the brain.

We have recently shown that loss of Zeb1 in adult neural stem cells of the hippocampus increases their neuronal output at the expense of glial cells (Gupta et al. Cell Rep 2021). This suggests a role for Zeb1 beyond stem cell maintenance in determining the type of cells produced by neural precursors, enabling the generation of glial cells, or suppressing an alternative neuronal fate. Interestingly, mature astrocytes also express Zeb1, which could indicate that Zeb1 regulates other astrocyte-specific functions.

The goal of this project is to determine if Zeb1 is necessary for glial cell production during development and to investigate its roles in mature astrocytes. To accomplish this goal, Zeb1 will be selectively eliminated from a subset of neural progenitors at different embryonic timepoints, before or around the time when glial cells start to be produced. The impact of Zeb1 loss on glial cell production will be analyzed postnatally by assessing number, position and morphology of glial cells. Those experiments will be complemented by comparative RNA-Sequencing analysis of wild type and Zeb-deficient progenitors and astrocytes, because as a transcription factor, Zeb1 can activate or inhibit the expression of other genes, depending on which cofactors it associates with. This analysis will shed light on the networks of genes controlled by Zeb1 across different cell types. Finally, to investigate the role of Zeb1 in mature astrocytes, Zeb1 will be selectively eliminated from astrocytes postnatally using mouse genetics. Number, position and morphology of astrocytes in different brain regions will be analyzed and results compared to the effect of removing Zeb1 before the onset of gliogenesis.

This project is an interdisciplinary collaboration between three laboratories with experiences in developmental neuroscience (Dr Martinez-Garay), stem cell biology (Dr Siebzehnrubl) and computational bioinformatics (Dr Zhou). All three will jointly supervise the project. Their laboratories are closely located and with access to state-of-the-art equipment (e.g., confocal and light sheet microscopy).