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Abstracts

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T13-020B

Foxg1 antagonizes neocortical stem cell progression to astrogenesis

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Neocortical astrogenesis follows neuronogenesis and precedes oligogenesis. Among key factors dictating its temporal articulation, there are progression rates of pallial stem cells (SCs) towards astroglial lineages as well as activation rates of astrocyte differentiation programs in response to extrinsic gliogenic cues. In this study, we showed that high Foxg1 SC expression antagonizes astrocyte generation, while stimulating SC self-renewal and committing SCs to neuronogenesis. We found that mechanisms underlying this activity are mainly cell autonomous and highly pleiotropic. They include a concerted downregulation of four key effectors channelling neural SCs to astroglial fates, as well as defective activation of core molecular machineries implementing astroglial differentiation programs. Next, we found that SC Foxg1 levels specifically decline during the neuronogenic-to-gliogenic transition, pointing to a pivotal Foxg1 role in temporal modulation of astrogenesis. Finally, we showed that Foxg1 inhibits astrogenesis from human neocortical precursors, suggesting that this is an evolutionarily ancient trait.

T13-021B

Neurogenic activation of striatal astrocytes after excitotoxic lesion: insights in the clonal dynamics of progenitor lineage progression

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In the adult brain two subsets of astrocytes act as neural stem cells (NSCs) in the canonical neurogenic niches of the sub-ventricular zone and hippocampal dentate gyrus. However, comparative studies and the analysis of specific pathological conditions have proven that new neurons can be generated also outside these niches, in the mature brain parenchyma. For instance, we reported that after excitotoxic lesion, subsets of striatal astrocytes undergo a spontaneous neurogenic activation leading to the generation of neuroblasts. Yet, it remained to be established how the striatal neurogenic niche is organized and what dynamics govern the activation and lineage progression of striatal astrocytes.
Here, through genetic lineage tracing and 3D reconstructions coupled with mathematical modelling we dissected

the transition of striatal astrocytes toward neurogenesis. In contrast to NSCs that cluster together in the canonical niches, activated astrocytes are scattered throughout the striatal parenchyma. Upon neurogenic activation, striatal astrocytes clonally expand generating independent cell clusters. Thus, numerous individual niches populate the striatum. Striatal astrocytes undergo activation with a constant rate, resulting in the constant addition of new striatal niches with time. However, the total number of niches does not appear to vary, indicating that individual niches have a transient existence. Of note, striatal niches are initially composed only by activated astrocytes and transient amplifying progenitor-like cells. These latter cells initially expand and then generate proliferating neuroblasts following a stochastic mode of division/differentiation. Newly generated neuroblasts first accumulate in the clusters, then become postmitotic, and subsequently disperse as individual cells. Thus, striatal neurogenesis occurs through the continuous and asynchronous transition of multiple neurogenic astrocytes from quiescence to an active state.
These data suggest that the neurogenic potential may be widespread among striatal astrocytes and that the striatal parenchyma is largely permissive for de-novo establishment of neurogenic niches.

T13-022B

GPNMB is a negative regulator of Oligodendrogenesis in the adult brain

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Neural stem cells residing in the subventricular zone (SVZ) of adult brains are a source of remyelinating oligodendrocytes. In particular, a subset of these cells which express the transcription factor Gli1 in the ventral SVZ, have been shown to migrate to demyelinating lesions and differentiate into oligodendrocytes in the corpus callosum. However in the healthy brain, these cells do not generate oligodendrocytes, instead they differentiate into neurons in the olfactory bulb. Using a transcriptomic analysis of neural stem cells, we identified a type-1 trans-membrane protein, Glycoprotein nonmetastatic melanoma protein B (GPNMB) as one of the genes responsible for the inhibition of oligodendrocyte generation in the adult brain. Our data shows that GPNMB is expressed in neural stem cells and not in the oligodendrocyte progenitor cells in the adult brain. Further, in vitro overexpression of GPNMB in the adult neural stem cells inhibits the generation of oligodendrocytes. These results suggest that GPNMB inhibits the differentiation of oligodendrocytes from adult neural stem cells and may help guide efforts to enhance remyelination.

T13-023B

The mitochondrial peptidase YME1L controls the early proliferative steps of adult neurogenesis

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The hippocampus is one of the few regions in the adult mammalian brain where neural stem cells (NSCs) give rise to new functional neurons, thus contributing to key aspects of cognition. This process involves the activation