Adult astrogenesis and functional astrocyte heterogeneity in the adult mouse hippocampus

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The brain works as a functional co-operation unit between neurons and glial cells. This unit differs in its physiological properties in distinct brain regions and developmental stages. Neuronal diversity has been extensively investigated in the last decades. Recent works now suggests that also astrocytes are molecularly and functionally distinct, yet still little is known about astrocyte heterogeneity. We found that the adult hippocampal dentate gyrus is populated by morphologically distinct astrocytes that are localized to specific compartments. In order to assess structural astrocyte heterogeneity we carried out a detailed morphological analysis of distinct astrocyte subtypes and assessed their “connectome”, i.e. which other niche cells and structures are in direct contact to the astrocytes. As structural heterogeneity of astrocytes may be a reflection of their functional properties, we performed single-cell sequencing of astrocyte subtypes to analyze distinct molecular properties of astrocytes and to identify new markers for targeting astrocyte subtypes.

In contrast to the prevailing assumption that astrocytes are postmitotic in the non-injured adult brain, our work revealed proliferation of non-radial astrocytes in the adult dentate gyrus. Even more surprising was the finding that morphologically distinct astrocytes show a differential proliferation response in the context of specific stimuli (voluntary exercise and ageing). These observations led to the hypothesis that the dentate gyrus is composed of molecularly and functionally distinct astrocytes whose dynamics are critical modulators for hippocampal adaption to changing conditions. Collectively, our study provides the first description of adult astrogenesis, structural heterogeneity and subtype-specific dynamics of astrocytes in the hippocampus.