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Differential effect of Dlx2 in neural precursors derived from the anterior and hippocampal SVZ

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Introduction:

Neural stem cells (NSCs) are self-renewing multipotent precursors capable of giving rise to both neurons and macroglia. NSCs persist postnatally in the subventricular zone (SVZ) the germinal epithelium lining the lateral ventricle. In the anterior SVZ (SVZa), three main types of precursors drive the process of neurogenesis (type B, C and A) leading to the generation of olfactory inhibitory interneurons throughout adulthood. Type B cells, the primary stem cell type divides rarely giving rise to type C cells or transit amplifying cells that by rapid divisions generate committed migratory neuroblasts also known as type A cells. Although both type B and C cells are clonogenic *in vitro* they can be distinguished on the basis of expression of glial fibrillary filament protein (GFAP) and distal homeobox transcription factor Dlx-2 respectively. Neuroblasts also express Dlx-2 however in contrast to type C cells they do not form clones and do not express epidermal growth factor receptor (EGFR). Recent reports have suggested that also the posterior hippocampal SVZ contains a similar cellular organization however the nature of these

precursors is poorly understood. Thus, EGFR+ cells derived from anterior and hippocampal SVZ were compared by clonal assay, gene expression level of EGFR and Dlx2 and effect of Dlx2 gene expression.

Materials and Methods:

NPCs were proliferated in NSA medium containing EGF (20 ng/ml), FGF-2 (10ng/ml) and B27 (2%). For differentiation, NPCs were cultured on poly-L-lysine (PLL)-coated chamber slides with NSA medium containing 1% FCS and 2 ng/ml FGF-2. Lentivirus was produced in 293FT cell line by cotransfection of lentiviral construct and packaging plasmids for Dlx2 gene delivery to NPCs. EGFR+ cells or infected cells were sorted by FACS. Gene expression level was analyzed by qPCR.

Results:

EGFR expressing cells were isolated from both the anterior and the hippocampal SVZ of postnatal and embryonic mice at day 18 of embryonic development (E18). Despite they were both capable of forming clones, cells derived from the hippocampal SVZ expressed

lower levels of EGFR and Dlx-2 mRNA and were less neurogenic compared to their SVZa counterpart. Forced expression of Dlx2 promoted clone forming capacity, proliferation, and neurogenesis in precursors derived from the SVZa but not in precursors obtained from the hippocampal SVZ. Importantly the effect of Dlx-2 overexpression in SVZa precursors was mediated by activation of EGFR.

Taken together, these data suggest that SVZa and hippocampal SVZ precursors are intrinsically different. Furthermore Dlx2 promotes transit-amplifying properties only in precursors derived from the SVZa.

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