of DA neurons, in particular for cell survival and fiber innervation. We further demonstrated Ret-induced expression of DAT in vitro.

Keywords: Ret receptor tyrosine kinase; Glial cell line-derived neurotrophic factor; Dopaminergic neuron; Antisense oligonucleotides

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ERK2 directs neural progenitor cell proliferation and differentiation

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The MAP kinases, ERK1 and ERK2, are the central elements of one of the most prominent signaling cascades transducing signals from the cellular environment to cytoplasmic and nuclear effectors. In the brain, the ERKs play critical roles in processes as diverse as neural differentiation, synaptic plasticity and learning. Furthermore, mutations within elements of the MAP Kinase signaling cascade underlie the pathology of numerous genetic developmental disorders, each of which presents with a form of mental retardation. Despite the importance of these proteins, the role of the ERKs in neural development and specifically the consequence of individual ERK1 and ERK2 ablation during early corticogenesis have not been studied. We have therefore examined the function of ERK2 in the developing telencephalon by conditionally inactivating this gene through expression of cre recombinase driven by the glial fibrillary acidic protein (GFAP) promoter. ERK2 is inactivated at embryonic day 13.5 within radial neural progenitor cells, which account for 90% of neurons and glia of the isocortex.

The deletion of ERK2 within the GFAP-expressing progenitors results in a substantial reduction in the thickness (20%) of the cerebral cortex. The postnatal brain of ERK2 Conditional Knockout (CKO) mice exhibits fewer neurons within all cortical lamina. Neural progenitor proliferation, evaluated through analysis of mitotic markers and acute BrdU labeling, is dramatically different in the CKO and wildtype brain. The dynamics of cortical neurogenesis are changed such that fewer neurons are born during the peak of neurogenesis. Correspondingly, CKO brains display more progenitor cells residing within the ventricular zone during later developmental periods. This enlarged pool of progenitors subsequently gives rise to an increased number of astrocytes during the gliogenic period, which populate the mature cortex. These data demonstrate that ERK2 specifically acts within the developing telencephalon as a proneural factor by regulating neural progenitor cell proliferation and differentiation.

Keywords: Neural progenitor cell; Neurogenesis; MAPK; Gliogenesis

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[P133]

Evolutionary comparison of *ER81* regulatory sequences responsible for cerebral-specific gene expression in mouse and zebrafish

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During evolution, the mammalian neocortex has acquired a laminar-specific organization, contrasting to the simpler, nuclear organization of the cerebral hemispheres in non-mammalian vertebrates. Strikingly, despite this structural divergence, cerebral-specific gene expression patterns have been conserved across vertebrate phyla. To better understand how gene regulatory sequences have co-evolved with the acquisition of a laminar organization, we are performing a cross-species analysis of the regulatory regions of *ER81*, an ets-domain transcription factor specifically expressed in layer V neurons in mouse versus a nuclear pattern in zebrafish. Recent studies have demonstrated that while cerebral expression of mouse (m) *ER81* is FGF-responsive, zebrafish (z) *ER81* does not require FGF-signalling (Roussigné and Blader, 2006). To further examine how *ER81* regulatory pathways have diverged, we have established an in utero electroporation procedure to test the activity of reporter constructs in the murine neocortex, validating this approach by testing the activity of a known laminar-specific enhancer. To initiate our analysis of m*ER81* regulatory elements, we first confirmed that misexpression of constitutively active (CA)-FGFR3 or CA-ras can induce ectopic m*ER81* expression in the murine neocortex. Secondly, we demonstrated that a 7.8 kb 5′-upstream fragment of m*ER81*, which contains five regions of 75% sequence similarity between mouse and human, drives reporter gene expression in the mouse neocortex, albeit not in a laminar-specific pattern. Currently, we are testing the activity and FGF-responsiveness of a recombined m*ER81* BAC containing 45 kb of upstream sequence. Finally, we have used this system to test the activities of a deletion series of zebrafish *ER81* reporter constructs, identifying a region between −1.5 and −2 kb upstream that drives cerebral expression in both mouse and zebrafish. Taken together these studies will allow greater insights into how the regulation of gene expression has diverged with the acquisition of a laminar organization of cerebral neurons.

Keywords: Neocortex; Laminar organization; ER81

Reference

Roussigné, Blader, 2006. Gene Exp. Patterns (Epub).

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