CEREBRAL CORTEX DEVELOPMENT IS COORDINATED BY MITOCHONDRIAL REACTIVE OXYGEN SPECIES

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The nervous system is particularly sensitive to reactive oxygen species (ROS) (1). Under physiological conditions, ROS regulate cell proliferation, neuronal differentiation, and synapse maintenance, indicating a key role of ROS in neuronal function and homeostasis. Moreover, mitochondrial ROS (mROS) generated by astrocytes regulate brain metabolism and behavior. Particularly, the reduction of astrocytic mROS in the adult alters neuronal structure and integrity leading to cognitive decline (2). However, the impact of mROS generation in the developing brain is unknown.

Here, we used mice genetically engineered to constitutively express a mitochondrial tagged enzyme catalase (mCAT) to downmodulate endogenous mitochondrial ROS generation (2).

We found higher levels of neuronal markers, TAU and MAP2, and increased neurite outgrowth in primary cortical neurons from mCAT, in comparison with wild-type (WT) neurons, at 3 days in culture. Then, mROS downregulation accelerated neuronal differentiation in vitro. Next, we evaluated whether the decreased mROS in the brain altered neurogenesis in vivo. Downregulation of mROS altered neurogenesis and layer organization in cerebral cortex from E15 mice. The proportion of cells expressing the progenitor cell marker NESTIN was lower, whereas that expressing neuronal markers TUJ1 and MAP2, was higher in the E15 mCAT cortices, compared to WT. Moreover, number of proliferating cells (BrdU-positive cells) in the ventricular/subventricular zones was lower, whereas immature neurons (TUJ-1 positive cells) were enriched in the interzone layer of E15 mCAT cortices, in comparison to WT. This was accompanied by an altered cortical radial distribution of MAP2 positive neurons in the cortex of E15 mCAT.

Our results suggest a key role of endogenous mROS levels in cell proliferation and neurogenesis onset, which would coordinate layer patterning in the cerebral cortex during brain development.

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