Investigating the cellular and molecular mechanisms impacting striatal development in a mouse knockout model of Dyrk1a

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Résumé

DYRK1A (Dual-specificity Tyrosine-phosphorylation Regulated Kinase 1A) is a kinase with a prevalent function in neuronal development and involved in numerous cellular processes including cell cycle control and cell viability. While DYRK1A overexpression leads to the neurodevelopmental defects in Down syndrome, its heterozygous loss of function leads to DYRK1A syndrome characterised by intellectual disability, microcephaly, developmental delay, autism spectrum disorders and epilepsy. Homozygous knockout (KO) of Dyrk1a in the mouse leads to early embryonic mortality, precluding studies of Dyrk1a function during later development. My internship laboratory generated a conditional KO mouse model for Dyrk1a to study its role in GABAergic neurons development. Conditional homozygous KO mice die shortly after birth. Furthermore, these mice exhibit striatal agenesis. Previous analyses have shown that postmitotic GABAergic neurons undergo apoptosis at the onset of neurogenesis in the conditional KO embryos. Additionally, the size of the progenitor proliferation zone is increased from the E16.5 stage onwards. The aim of my internship project is to identify the molecular and cellular mechanisms involved in neuronal cell apoptosis and in the impact on progenitor cell proliferation observed in the embryos. I have performed Western blot quantifications of proteins from different pathways leading to cell apoptosis, survival and cycle regulation to identify which pathway(s) is/are affected by Dyrk1a loss-of-function. I will also analyse the cell cycle via immunohistochemistry to investigate how the proliferation of neural progenitor cells is affected.

Mots-Clés: DYRK1A, GABAergic neurons, apoptosis, cell cycle, striatum

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