Dyrk1a dosage in Cortical Interneuron Migration : insights for DYRK1A and Down Syndromes

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Résumé

Proper development of excitatory and inhibitory neural systems is essential for normal brain function. Disruptions in the balance between these systems are a hallmark of various neurodevelopmental disorders, including Down syndrome (DS) and DYRK1A-haploinsufficiency syndrome (DHS). In DS, the excitatory/inhibitory imbalance is commonly attributed to gene dosage effects, particularly involving *DYRK1A*, a gene located on chromosome 21. While *DYRK1A* overexpression has been implicated in altered neurogenesis and intellectual disability, its role in GABAergic interneuron development remains underexplored. Conversely, DHS is caused by gene mutations and is associated with epilepsy, intellectual disability, and autism spectrum disorder, suggesting that both increased and decreased dosage of *Dyrk1a* can impair GABAergic circuit formation.
In this study, we investigated how *Dyrk1a* dosage affects the migration of GABAergic interneurons originating from the medial and caudal ganglionic eminences. Using mouse models combined with time-lapse imaging, we analyzed key migratory parameters, including speed, pausing behavior and nucleokinesis dynamics. In parallel, we assessed morphological changes of migrating interneurons, such as leading process extension and branching.

We found that *Dyrk1a* critically control GABAergic interneuron migration and alterations in its dosage lead to convergent migratory phenotypes. Both overexpression and haploinsufficiency result in reduced migratory efficiency, characterized by decreased speed, increased pausing and impaired nucleokinesis. These shared defects are accompanied by common morphological alterations, including unstable leading processes. In addition, increased branching leads to a more complex morphology of migrating interneurons, which likely interferes with directional persistence and efficient nucleokinesis.

Mechanistically, we identify that these migratory defects are linked to the dysregulation of *Dyrk1a* downstream targets controlling actomyosin dynamics. In the DHS model, altered phosphorylation of key cytoskeletal regulators leads to impaired actomyosin contractility, thereby disrupting nucleokinesis. These findings uncover a molecular pathway through which *Dyrk1a* dosage controls the cytoskeletal machinery required for efficient interneuron migration.
Together, our findings highlight a critical requirement for precise *Dyrk1a* dosage in regulating interneuron migration by controlling actomyosin-dependent cytoskeletal dynamics, with important implications for neurodevelopmental disorders.

Mots-Clés: Neurodevelopment, DYRK1A, Interneuron, Cortex, Down syndrome

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