Deciphering the Mechanisms involved in Interneuron-Oligodendrocyte Precursor Cell Crosstalk in the Developing Cortex – from Mouse to Human

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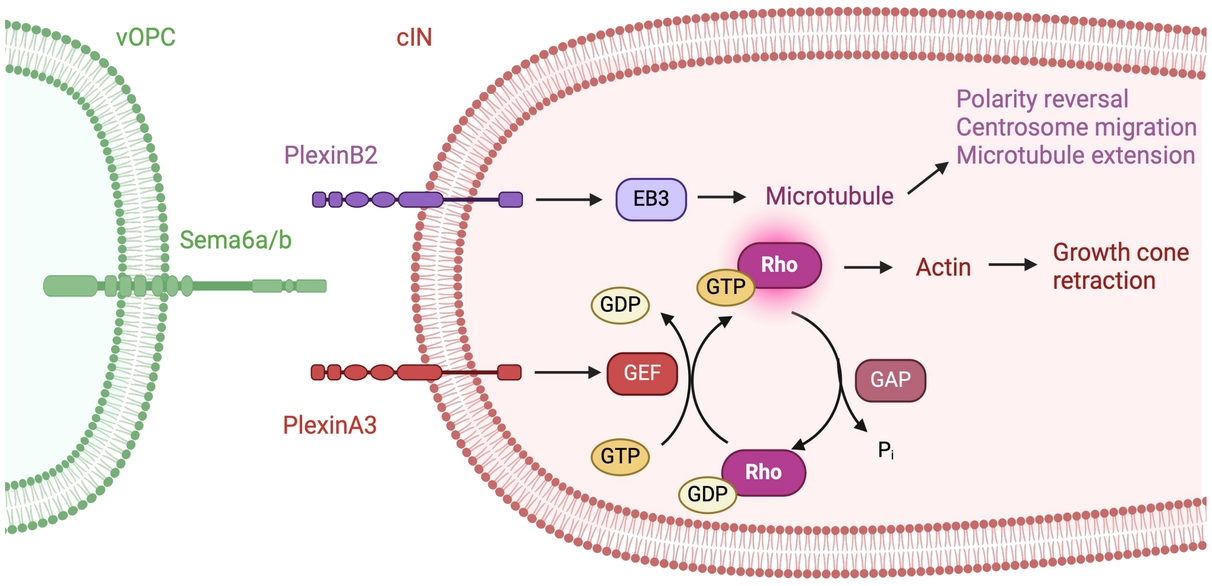
Introduction

During embryogenesis, various neural cell types are generated and migrate to reach the developing cortex. This process involves intricate crosstalk between different cell populations, influencing their migration, maturation, and integration into neural networks. Notably, during early embryonic stages, an interaction between oligodendrocyte precursor cells (OPCs) and cortical interneurons (cINs) named unidirectional contact repulsion (UCoRe) guide cINs within migration streams and prevents their accumulation around blood vessels (BVs). In mice, this mechanism involves an interaction between the transmembrane Sema6a/b expressed by OPCs and Plexin A3/B2 expressed by cINs, potentially regulating actin and microtubule dynamics. However, the conservation of UCoRe between OPCs and cINs across other gyrencephalic species is unknown. To address this question, lentivirus infections were conducted targeting the medial ganglionic eminences (MGE) of humans and ferrets throughout the first trimester. Our preliminary results suggest a conservation of UCoRe mechanism in gyrencephalic species. However, the underlying mechanism remains to be further elucidated. This study will allow us to understand the importance of the crosstalk established between OPCs, INs and BVs during UCoRe with an Evo-Devo perspective.

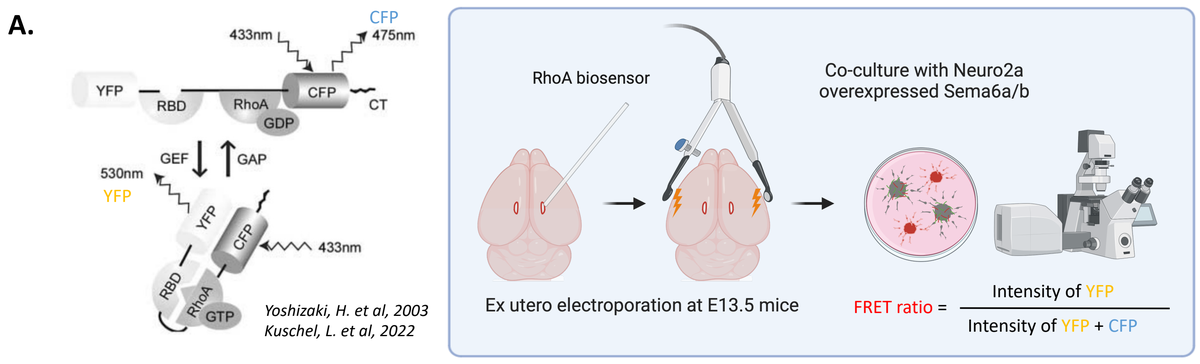
Outline



1/ Decipher the molecular mechanisms acting downstream UCoRe in INs by assessing MT and actin dynamics

2/ Assess the interaction between vOPCs and INs across species

FRET microscopy to measure the dynamics of RhoA in cINs during UCoRe



A. According to the literatures, PlexinA3 can modulate actin dynamics through RhoA GTPase. To better understand the link between actin and plexin in cINs, live imaging of RhoA will be performed using genetically encoded FRET-based RhoA biosensor.
B. The preliminary results demonstrated a higher FRET ratio intensity in cINs during contact of their leading process with OPCs, which decreased upon retraction of the cIN leading process, suggesting RhoA dynamic changes. (Mice E13.5, N=1, 3 cells in each group)

Acknowledgement

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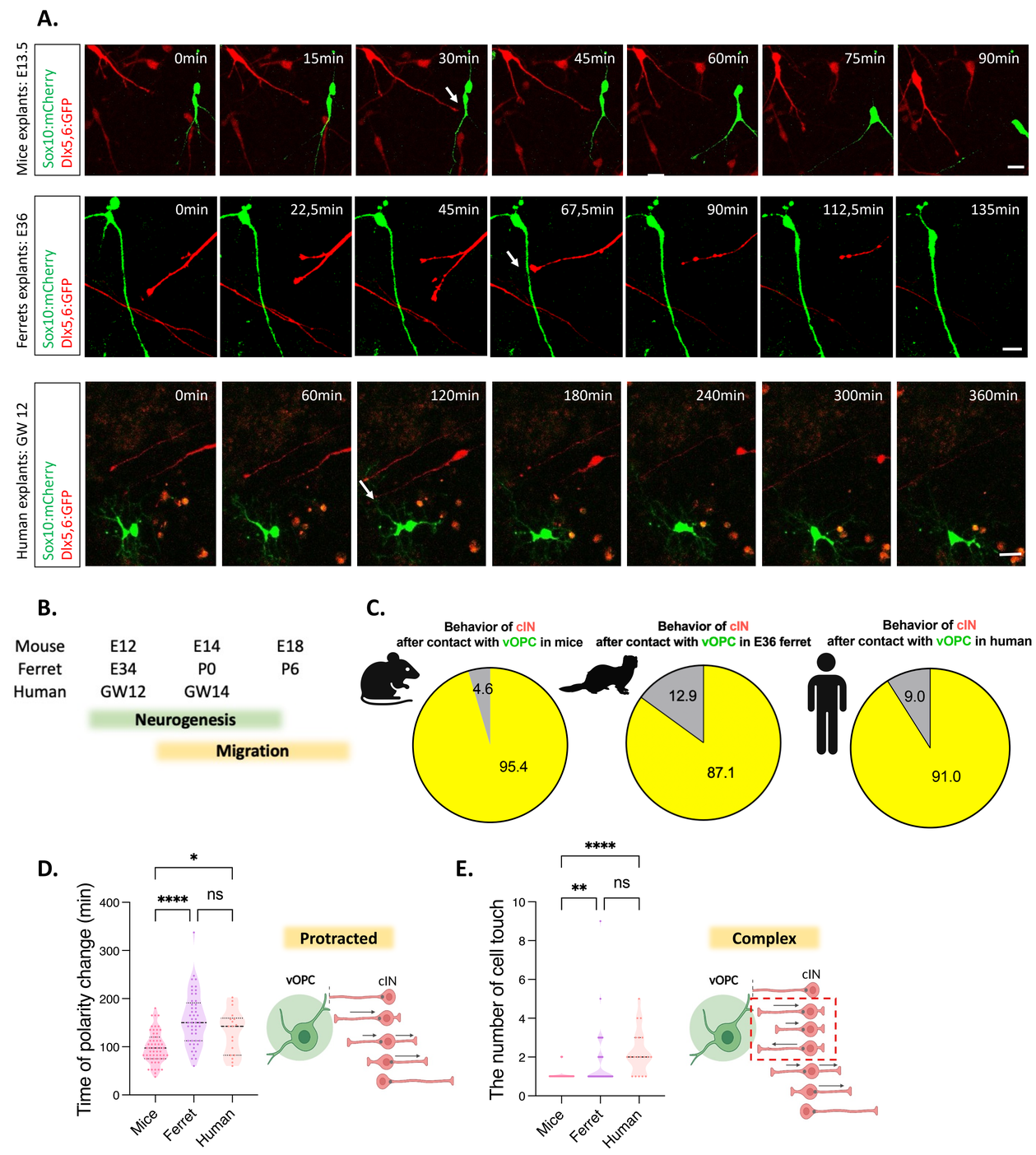
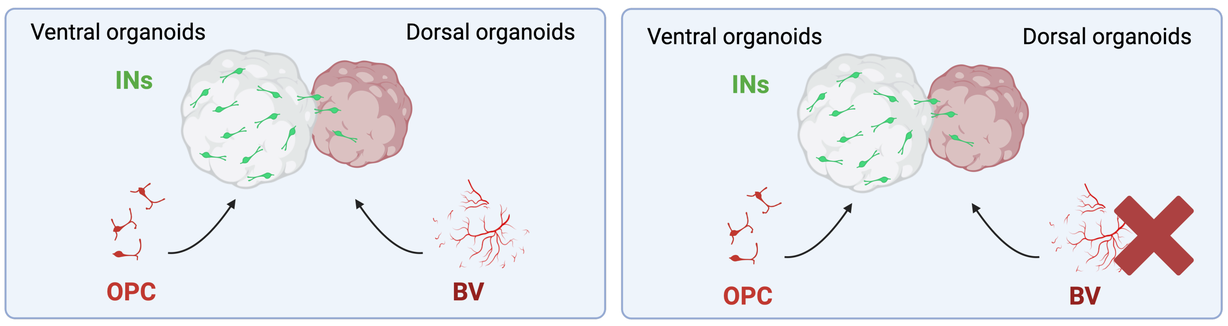
UCoRe is conserved across species



A. To test whether UCoRe is conserved in ferrets and humans' forebrain, we performed explants of MGE and infected with lentiviruses expressing sox10:mCherry (to label vOPCs) and dlx5,6:GFP (to label cINs) and imaged by time-lapse recording.
B. Corresponding ages between species during development.
C. The occurrence of UCoRe was observed at 95.4% in mice, 87.1% in ferrets, and 91% in humans.
D. The average time for polarity change is 98.53 minutes in mice, 156.7 minutes in ferrets, and 130.2 minutes in humans. The time of polarity change increase across species.
E. The number of leading process touches between cINs and OPCs increase across species.

The role of BVs within UCoRe in 3D human brain assembloids



Given the three-party (neuron-glia-vascular) interaction where vOPCs interact with both BVs and cINs, we hypothesize that the interaction between vOPCs and BVs may prime the interaction between vOPCs and cINs. To investigate this hypothesis, we will generate 3D human brain assembloids incorporating hiPSC-derived OPCs and endothelial cells to monitor and test the interactions between cINs and vOPCs both in the presence and absence of BVs by time-lapse recording.

Conclusion

1/Preliminary results showed that RhoA activity changes in cINs during UCoRe, as observed using FRET-based RhoA biosensor time-lapse recordings, indicating RhoA GTPase pathway may be recruited during UCoRe.
2/UCoRe can be observed in mice, ferrets, and humans. The time of polarity change is significantly protracted across species. Moreover, the number of leading process touches between cINs and OPCs before induction of UCoRe are significantly increased across species. These results suggest that UCoRe become more complex across species. We plan to do snRNA-seq across species uncover additional downstream intracellular pathways beyond those already identified in mice.