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A Quantitative Framework to Evaluate Modeling of Cortical Development by Neural Stem Cells

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SUMMARY

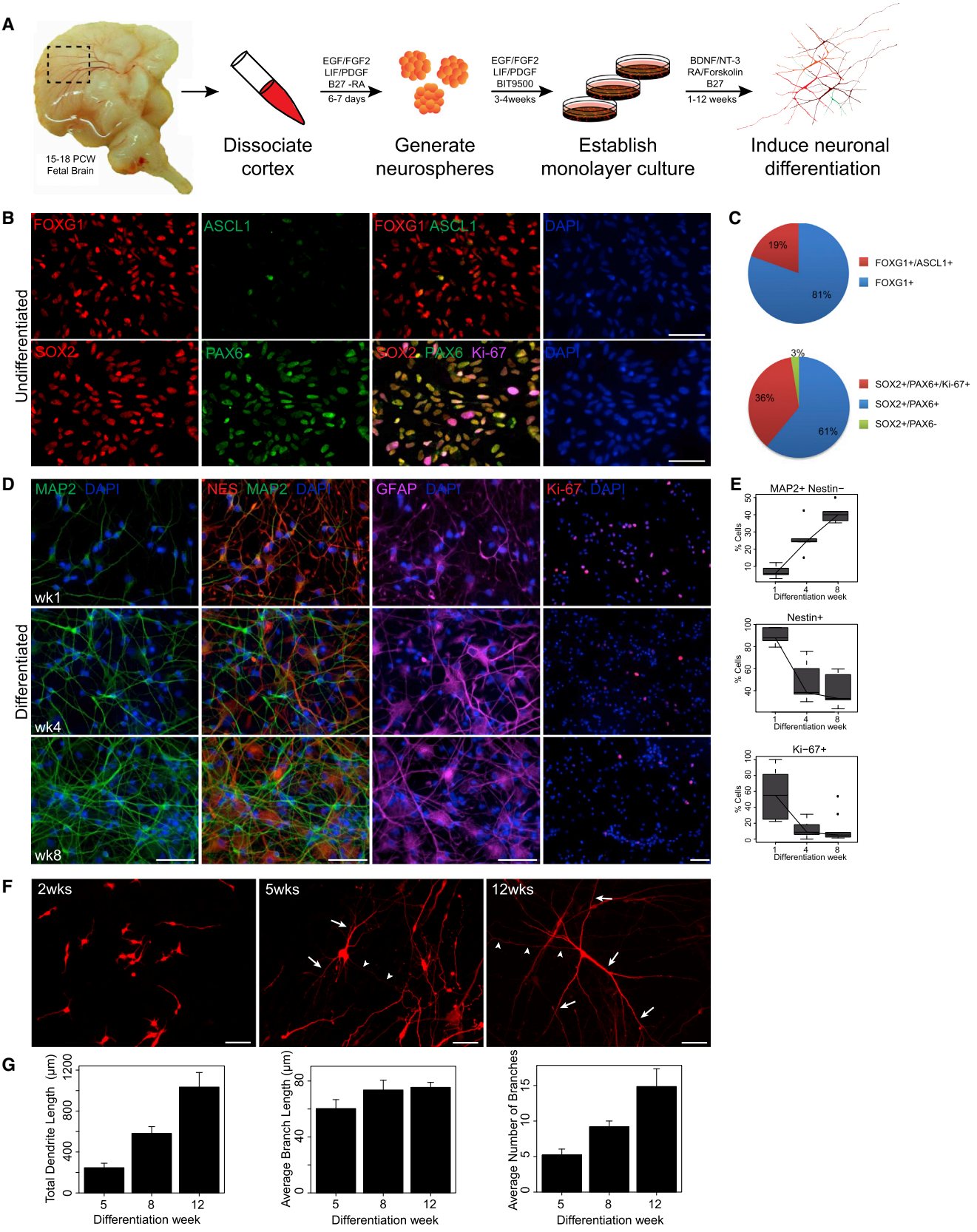
Neural stem cells have been adopted to model a wide range of neuropsychiatric conditions in vitro. However, how well such models correspond to in vivo brain has not been evaluated in an unbiased, comprehensive manner. We used transcriptomic analyses to compare in vitro systems to developing human fetal brain and observed strong conservation of in vivo gene expression and network architecture in differentiating primary human neural progenitor cells (phNPCs). Conserved modules are enriched in genes associated with ASD, supporting the utility of phNPCs for studying neuropsychiatric disease. We also developed and validated a machine learning approach called CoNTExT that identifies the developmental maturity and regional identity of in vitro models. We observed strong differences between in vitro models, including hiPSC-derived neural progenitors from multiple laboratories. This work provides a systems biology framework for evaluating in vitro systems and supports their value in studying the molecular mechanisms of human neurodevelopmental disease.

INTRODUCTION

Human neural stem cells are poised to revolutionize our ability to make mechanistic inferences, bridging the gap between traditional model systems and human biology (Dolmetsch and Geschwind, 2011; Merkle and Eggan, 2013). Ideally, such a platform should maximize translational potential by recapitulating in vivo brain development and function as much as possible. Human embryonic stem (hES), induced pluripotent stem (hiPS), and primary human neural progenitor (phNPC) cells all have the ability to differentiate into functional neurons (Espuny-Camacho et al., 2013; Hansen et al., 2011; Palmer et al., 2001; Sandoe and Eggan, 2013). In each of these systems, disease-related processes can be modeled and studied by either generating hiPSCs from patients with known mutations or introducing genetic modifications into control neural stem cell lines (An et al., 2012; Brennand et al., 2011; Israel et al., 2012; Marchetto et al., 2010; Paşca et al., 2011; Rosen et al., 2011; Ryan et al., 2013; Soldner et al., 2011). Despite many options, there is neither a clear consensus as to which system or culture conditions are better suited to model aspects of neurodevelopment and disease nor a rubric for answering this question. The following have not been demonstrated using a rigorous genome-wide statistical framework: (1) how well in vitro models match in vivo development, (2) what level of developmental maturity is achieved after differentiation, (3) what neuroanatomical identity is modeled, (4) what specific neurodevelopmental processes and molecular mechanisms are preserved, and (5) what specific aspects remain to be better modeled in vitro, providing a guide for future work optimizing in vitro systems.

Recent large-scale efforts to measure the transcriptome from postmortem human brain provide an unbiased in vivo standard to which in vitro systems can be compared. These data sets measure gene expression at time points from embryonic to late adulthood and across several cortical and subcortical regions (Kang et al., 2011). In addition, gene expression in microdissected cortical laminae has been measured at mid to late fetal time periods (Miller et al., 2014), providing data sets with increased spatial resolution within a restricted developmental window.

Here, we develop and demonstrate genome-wide methods to quantify the similarity between in vitro neural stem cell models and brain development in vivo and apply them to a newly generated set of phNPC lines. We demonstrate remarkable preservation of neurodevelopmental processes spanning embryonic to fetal corticogenesis in phNPCs in vitro. But, even after months



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