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Deriving consecutive building blocks of human cortical development from pluripotent stem cells: Fundamentals and implications

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Modeling key cell fate decisions and heterogeneity during the establishment and ontogeny of cortical neural progenitors is fundamental for revealing origin of diverse lineages, identifying molecular forces regulating distinct potencies and developing strategies for generating homogeneous cortical neural stem cell (NSC) populations for regenerative medicine. Here we report our recent progress in developing such approaches and their implications. We isolated consecutive neural progenitors derived from human pluripotent stem cells (PSCs) differentiated along cortical development based on their notch activation state. We first isolated notch active CNS neuroepithelial cells exhibiting high proliferation and broad potential. These successively yield early and mid cerebral neurogenic radial glia followed by gliogenic radial glia, together recapitulating hallmarks of NSC ontogeny, cortical lamination and glial transformation in notch dependent manner. We used isolated stages as modules to identify forces driving cell fate transitions. We employed gene expression analysis and epigenetic profiling combined with computational approaches to infer key regulators progressively remodeling the epigenetic landscape and followed by shRNA functional validation. This allowed uncovering a core gene regulatory network of stably expressed transcription factors that dynamically interacts with stage specific factors to regulate cortical NSC fate transition. We further used these data to identify dynamics of pathway activation during this process and based on these we developed a streamlined and robust protocol for efficient cortical cell fate conversion from naive and primed PSCs using small molecules. We also used this method to efficiently develop cerebral organoids that are homogeneous for cortical regional fate and stem cell state. To exemplify the utility of the new protocol to model disease, we generated a microcephaly PSC line by introducing an autosomal recessive microcephaly mutation. We observed dramatic differences in microcephaly vs. WT organoids that were only apparent when specifically derived by our new protocol. We further identified abnormal cortical layer lamination and precocious differentiation in microcephaly organoids accompanied by cytoarchitectural and cellular defects, hence leading to a novel delineation of early pathology of microcephaly in cortical NSCs.

Biography

Yechiel Elkabetz has earned his BSc, MSc and PhD in Cell Biology from Tel Aviv University. He has started his investigation of human pluripotent stem cells (PSCs) and neural stem cells (NSCs) in 2004 at Lorenz Studer group at Sloan-Kettering Institute, NY. His study at the Sloan led to the isolation of a novel early type of NSCs termed rosette neural stem cells, which became a platform for understanding early neural specification events *in vitro*. In 2009, he established his lab at Tel Aviv University.

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