Instituts thématiques Inserm Institut national de la santé et de la recherche médicale

Institute of Psychiatry and Neuroscience of Paris

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Psychiatry and Neuroscience Seminar

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(Host C Hanus)

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A stem cell platform to map cell type and stage-specific cis-regulatory variation in mouse embryonic brain development

Wednesday, September 6th, 2023, noon

Room D Levy, 102-108 rue de la santé - 75014 Paris & VISIOCONFERENCE

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Over evolutionary timescales, natural selection has shaped the gene regulatory networks that control neuronal cell fate specification and terminal differentiation, leading to changes in neural circuit formation, function, and ultimately behavior across mammals. However, it remains difficult to parse the specific genetic changes that contribute to these differences and to define the developmental mechanisms at the molecular and cellular level. Neural organoids generated from pluripotent stem cells have emerged as a powerful model system for mechanistic dissection of brain development. Here, we generated induced pluripotent stem cells from F1 hybrid crosses between standard laboratory mice (C57Bl/6J) and four wild-derived inbred mouse strains (PWK/PhJ, MOLF/Ei, CAST/Ei, SPRET/Ei) from distinct sub-species spanning >1.5 million years of evolutionary divergence. To examine brain development in these mice, we developed a rapid and reproducible protocol to generate cerebral cortical organoids from mouse epiblast stem cells. Mouse cortical organoids develop with kinetics that mirror the embryonic cortex in vivo, generating cortical neurons, astrocytes, and oligodendrocytes over ~10 days. We have generated cortical organoids from each of these F1 hybrid lines and are mapping cell type and stage-specific changes in gene regulation in developing cortical cell types using single-cell RNA-seq and allele-specific read mapping. These data will provide insight into how changes in transcriptional regulation contribute to differences in cortical cell fate specification and establish mouse cortical organoids as a new model for studying the impact of cis-regulatory variation on cortical development.

Keywords:

Neurobiology | Cellular Neuroscience | Molecular Neuroscience | Neuroimaging

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