Examining the Contribution of Mitochondria During Human Neurogenesis Using Human Pluripotent Stem Cell-Derived Systems

By

Alejandra Inés Romero Morales

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Approved:

	Signature	Date
Ethan Lee, M.D., Ph.D.		01/31/2022
Vivian Gama, Ph.D.		01/31/2022
Rebecca Ihrie, Ph.D.		01/31/2022
Kevin Ess, M.D, Ph.D.		Jan 31st 2022
Jeffrey Rathmell, Ph.D.		

Summary

The brain is one of the most complex and mysterious organs in the human body. Centuries of research have shown that it is generated by a finely orchestrated series of events that take place in the first weeks of life up to early adulthood. How does a cluster of cells acquire the fate necessary to generate millions of neurons, astrocytes, and oligodendrocytes? Our laboratory proposes that mitochondrial homeostasis provides guidance to the intrinsic developmental programs of neuro and corticogenesis, while also being responsive to environmental and intercellular signals. To address this hypothesis, I utilize 2D and 3D platforms to interrogate the capacity of cells to generate neuronal and glia progeny in a background of metabolic dysregulation. In Chapter 2, I discuss the generation of Spinœ, an optimization of published bioreactors. We addressed deficiencies perceived by the use of the original design and proposed changes that not only increased the lifespan of the bioreactor but also optimized the generation of cerebral organoids for our laboratory. The effects of dysregulation of the mitochondria are analyzed in Chapter 3. We generated and characterized three commercially available fibroblast cell lines from Leigh Syndrome (LS) patients. LS is a fatal neurometabolic disease that is characterized by defective energy production, with highly metabolic tissues such as the brain being deeply affected. We generated iPSCs from these fibroblasts and analyzed their capacity to generate neuronal lineages in 2D and 3D models. I discovered that the causing mutations affect the generation of upper cortical neurons in all phenotypes and that this dysregulation could be mediated by the deficient switch of the LS-derived neurons to transition from a glycolytic state to an aerobic respiration paradigm. Finally, Chapter 4 highlights the use of brain organoids as a model system to interrogate the required mitochondrial changes necessary for brain development and how this system can be used to assess the effects of mitochondrial health during corticogenesis.