Rational derivation of DA neuron subtypes from iPS cells for improved modelling of Parkinsons disease

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Country

USA

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Rational derivation of DA neuron subtypes from iPS cells for improved modelling of Parkinsons disease

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5

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

Derivation procedure, pars compacta, dopaminergic neuron, induced pluripotent stem cell, Substantia nigra structure

Research Abstract

? DESCRIPTION (provided by applicant): Dopamine (DA) deficiency, caused by DA neuron degeneration, underpins the devastating motor symptoms of Parkinson's disease (PD). DA neurons located in the ventral tier of the substantia nigra pars compacta (SNc), are particularly vulnerable, compared to those in the dorsal tier of the SNc or ventral tegmental area (VTA). Why these DA neurons display differential vulnerability remains enigmatic. Understanding the underlying mechanisms would shed light on degeneration as well as potential neuroprotective strategies to mitigate the disease. iPS-derived DA neurons are an important new method for modeling PD. Yet current protocols for generating DA neurons are not designed to generate specific DA subtypes, a critical requisite for modeling selective vulnerability. This gap exists because the molecular heterogeneity of midbrain DA neurons is not well understood. To elucidate the heterogeneity of DA neurons, we have recently used single cell molecular profiling, coupled with anatomical co-labeling studies, and revealed the existence of at least six distinct of DA neuron subtypes in mouse models. Here, we aim to use this knowledge to i. better understand DA neuron diversity in vivo ii. understand mechanisms that may influence the generation of DA neuron subtypes iii. derive and characterize two prominent DA neuronal subtypes, one located in the SNc and one in the VTA, from human iPS cells in a rational manner, and iv. use these DA neuron subtypes to examine selective vulnerability in the context of genetic PD mutations. In Aim1, we will examine how Wnt signaling may influence DA neuron subtype allocation. In Aim 2, having optimized the Wnt regimen, we will next use targeted gene manipulations to derive highly enriched cultures of two specific DA neuron subtypes, and then characterize those subtypes by physiological and transcriptomic approaches. Next, we will generate both DA neuron subtypes from iPS cells harboring a DJ-1 mutation and examine differential pathological effects on both, SNc as well as VTA DA neuron subtypes. In Aim 3, we will further characterize the phenotype of the two DA neuron subtypes in vivo. We will elucidate the projections, and complete transcriptomes of two murine DA neuron subtypes, taking advantage of genetically targeted mice. Information from this aim will further highlight the differences between these subtypes. Additionally, these results will feed back into Aims 1 and 2, to further optimize our DA neuron subtype derivation protocol. In sum, taking advantage of the combined expertise and extensive interactions of two labs, we propose a cohesive plan based on molecular logic, to derive distinct DA neuron subtypes from iPS cells and aim to improve modelling PD. These studies will open the future possibility of understanding the effects of a range of PD mutations on selective vulnerability.

Lay Summary

PUBLIC HEALTH RELEVANCE: Our goal is to generate distinct DA subtypes from iPS cells towards understanding selective vulnerability of ventral tier substantia nigra neurons in Parkinson's disease.

Further information available at:

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Investments > €500k

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United States of America

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