Editorial

Stem Cell INVESTIGATION

Personalized medicine in a dish: the growing possibility of neuropsychiatric disease drug discovery tailored to patient genetic variants using stem cells

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Provenance: This is an invited Editorial commissioned by Editor-in-Chief Zhizhuang Joe Zhao (Pathology Graduate Program, University of Oklahoma Health Sciences Center, Oklahoma City, USA).

Comment on: Lorenz C, Lesimple P, Bukowiecki R, *et al.* Human iPSC-derived neural progenitors are an effective drug discovery model for neurological mtDNA disorders. Cell Stem Cell 2017;20:659-74.e9.

Received: 06 October 2017; Accepted: 27 October 2017; Published: 16 November 2017.

doi: 10.21037/sci.2017.10.05

View this article at: http://dx.doi.org/10.21037/sci.2017.10.05

The mechanistic links between patient genotype and the phenotypic changes associated with neuropsychiatric disease have been difficult to establish, owing in part to the lack of live brain tissue from clinical cases. In fact, for many brain disorders, it remains unclear whether disease progression reflects developmental aberrations during neural differentiation or activity-dependent perturbations in mature neurons. Fortunately, the ability to reprogram cells from patients and healthy controls into human induced pluripotent stem cells (hiPSCs) (1) has conferred the ability to generate a nearly limitless source of genetically matched human neural cells with which to model neuropsychiatric disease across a variety of neural cell fates. Already, hiPSC-based models have provided molecular and cellular insights into disease mechanisms underlying far-ranging brain disorders from autism spectrum disorder (2) to schizophrenia (3), Alzheimer's disease (4), Parkinson's disease (5), and even zika-virus induced microcephaly (6). These models are being increasingly applied to drug screening, successfully identifying compounds to enhance neural proliferation (7), modulators of lithium signaling (8) and inhibitors of zika virus infection (9). While many of these early screens have been conducted on neural progenitor cells (NPCs), screening has recently been extended to stem cell-derived neurons and astrocytes (10-12).

Because work by ourselves and others demonstrate that current hiPSC differentiation strategies yield neurons that most resemble fetal brain cells (13-16), hiPSC-based models remain best suited for the study of disease predisposition. Consistent with this, hiPSC-based studies of late onset neurodegenerative diseases such as Parkinson's disease (5), Alzheimer's disease (4) and amyotrophic lateral sclerosis (17) have failed to recapitulate the severe neuronal loss observed in human disease. Simply put, neural cells generated from patient-specific hiPSCs capture the genetic risk factors, known and unknown, that a given individual was born with, but fall short of modeling the complex cellular interactions and circuit-based activity that contribute to disease initiation or progression. As a result, we and others have developed and validated models of autism spectrum disorder (18), schizophrenia (13,19,20), bipolar disorder (21), Parkinson's disease (22) and Huntington's disease (23) that focus on the molecular and cellular defects in immature NPCs, rather than post-mitotic neurons, consistently observing that at the level of gene pathways and networks, gene expression differences identified in patient neurons are frequently conserved in patient NPCs (13,24).

NPCs are a scalable cell type, amenable to parallel culture of dozens of cell lines and highly adaptable to automated methods. They are straightforward to maintain *in vitro*, requiring less frequent feeding and passaging than their source hiPSCs (25). NPCs proliferate robustly, are cryopreservable, and easily differentiated or induced to mature neurons (25,26) and astrocytes (27). Overall, NPCs

are an ideal cell type for mechanistic studies of disease biology as well as adaptation to high throughput drug screens.

Current hiPSC models of neuropsychiatric disease have generally focused on those risk factors encoded in the nuclear DNA sequence, with little consideration of epigenetic regulation and no understanding of mitochondrial biology [reviewed in (28)]. While it is well established that highly penetrant nuclear genome mutations can recapitulate neuropsychiatric disease biology, it has been unclear, to date, to what extent hiPSC-based models also capture the effects of mitochondrial disease risk. In fact, although it was previously established that mitochondria undergo morphological and metabolic reconfigurations while donor cells are being reprogrammed to hiPSCs (29) and hypothesized that mitochondrial state was linked to cellular differentiation (30), it was unclear to what extent cell-type specific mitochondria activity patterns would be re-established during neuronal differentiation.

Now, Lorenz et al demonstrate that disease- and genotype-specific mitochondrial risk effects can also be modeled with hiPSCs. Over the course of neuronal differentiation from hiPSCs, mitochondria shift toward a neuronal-like oxidative metabolism. hiPSC-derived NPCs derived from three patients with homoplasmic mitochondrial mutations in *MT-ATP6* not only retained the mutant genotype, but also exhibited disease relevant phenotypes such as decreased ATP production, abnormally high mitochondrial membrane potential, and altered calcium homeostasis (31). Moreover, as a proof-of-concept, they successfully screened 130 drugs on NPCs derived from one of these patients, identifying ten compounds that significantly reduced mitochondrial membrane potential (31). While it is premature to speculate whether these drugs represent novel therapeutics for mitochondrial disease, this is an exciting demonstration that hiPSC-based models can provide novel insights into mitochondrial disorders.

A critical limitation of hiPSC-based models is that the genotype in the donor somatic cells (typically skin or blood) accurately reflects what is observed in the tissue impacted by disease. At the level of nuclear DNA, hiPSC-based models fail to accurately model the impact of somatic mosaicism, either because: (I) the genotype of the donor cells is different from the brain; (II) the hiPSC-derived neural cells spontaneously differ from that of the donor cells (32); or (III) the mosaic variants are selected for or against during the reprogramming or differentiation processes causing the hiPSC-derived neural composition to inaccurately reflect that found in the brain (33). Variation between mitochondrial populations in donor cells, disease cells and hiPSC-derived populations remains a similar concern for mitochondrial disorders. Although it is clear that a homoplasmic mitochondrial population can be accurately maintained and modeled using hiPSC-based models (31), the extent to which that is true for heteroplasmic mitochondrial disorders is unknown.

Since the first discovery that patient somatic cells can be reprogrammed to hiPSCs that are theoretically capable of generating all the cell types of the human body, our ability to model the impact of genetic risk on disease phenotypes continues to advance. Now, with the knowledge that mutations in either the nuclear or the mitochondrial genome can be modeled as well as screened against using hiPSCs, our ability to uncover novel disease mechanisms and therapeutics for neuropsychiatric disease continues to expand.

Acknowledgements

Funding: KJ Brennand is a New York Stem Cell Foundation-Robertson Investigator. This work was partially supported by National Institute of Health grants R01 MH101454, as well as the New York Stem Cell Foundation and the Brain Behavior Research Foundation.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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doi: 10.21037/sci.2017.10.05

Cite this article as: Brennand KJ. Personalized medicine in a dish: the growing possibility of neuropsychiatric disease drug discovery tailored to patient genetic variants using stem cells. Stem Cell Investig 2017;4:91.