

A Short Note on Pluripotent Stem Cells in Psychiatry

Abstract

The creation of high-fidelity model systems that can be experimentally manipulated to investigate and test the pathophysiological mechanisms of illness is a major obstacle in psychiatry research. In this regard, the arising ability to determine brain cells and circuits from human actuated pluripotent undifferentiated organisms (iPSCs) has produced critical energy. In the context of other technical approaches that are currently available, the purpose of this review is to provide a critical evaluation of the potential for iPSCs to illuminate pathophysiological mechanisms. We talk about how to choose iPSC phenotypes that are relevant to psychiatry, the data that researchers can use to help them make these choices, and the differences between using 2-dimensional cultures and more complex 3-dimensional model systems. We talk about the challenges and opportunities presented by current models, as well as their advantages and disadvantages. In conclusion, we talk about the steps that will need to be taken to ensure that robust and reliable conclusions can be drawn and the potential of iPSC-based model systems for elucidating the mechanisms underlying genetic risk for psychiatry. We contend that while iPSC-based models are obviously positioned to concentrate on major cycles happening inside and between brain cells, they are frequently less appropriate for case-control studies, given issues connecting with measurable power and the difficulties in recognizing which cell aggregates are significant at the level of the entire person. Our point is to feature the significance of considering the speculations of a given report to direct choices about which, if any, iPSC-based framework is generally proper to address it.

Keywords: Pluripotent stem cells • Psychiatry • Neuropathological changes

Introduction

Mechanistically, psychiatric disorders are difficult to study because they are unique to humans and arise from the complex dysfunction of a largely inaccessible tissue. As a result, putative brain cells that are derived from human induced pluripotent stem cells (iPSCs) have been enthusiastically adopted as potential model systems due to the fact that they possess the genomes of actual people and can be experimentally manipulated. Their potential benefits and applications, both in clinical settings and as research tools, are the subject of numerous recent reviews. However, few have attempted to situate them in the broader technical and conceptual landscape of psychiatric research and critically evaluated their use. In this paper, we attempt to do so and offer some advice on how to plan and report iPSC studies in psychiatry.

As we'll see below, iPSC systems are perfect for studying fundamental cellular and molecular processes as well as possible aspects of neurodevelopment. However, their use in other contexts is significantly less clear. This is especially true for studies that try to connect cellular measurements to psychiatry-relevant phenotypes in the whole person, which are usually complex and change over time. Some of these difficulties are solely logistical, like the need for a sufficient sample size and statistical power, while others are more conceptual; for example: How do we determine which phenotypes, if any, are meaningful, even when strong relationships between phenotypes at the cellular and whole-individual levels are observed? We advise both new and seasoned iPSC researchers to return to their hypothesis and ask themselves these fundamental questions: What do you want to model, and is the iPSC platform that has been suggested capable of achieving this with high fidelity? If iPSC-based systems are able to assist in separating what is meaningful from

Tom Wilson*

Department of Neuroscience & Physiology
Zambia

*Author for correspondence:

Wilson_tom@gmail.com

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what is merely possible, we believe that reflecting on these questions is essential.

The creation of three-dimensional (3D) cultures, also known as brain organoids or spheroids, is a more recent development. A couple of studies have looked at 3D models got from patients [with mental imbalance, schizophrenia, or bipolar problem versus control subjects. Organoids are being used by researchers to study how genes with rare, penetrant mutations associated with disorders affect neurogenesis and gene expression. It is likely that studies using organoids will become more prevalent due to their appeal as a potential window into human neurodevelopment and the early stages of psychiatric disorder pathology. However, the majority of psychiatric organoid experiments are essentially proof-of-principle studies because they are conducted on a small scale [1-5].

Discussion

In the context of a specific human cell with a specific human genome, iPSC models have the potential to approximate biological aspects of illness or risk. These models can then be studied to illuminate pathogenic mechanisms and to identify targets for remediation or rescue. Finding the most suitable phenotypes to measure and cell types to study is, without a doubt, the greatest obstacle to realizing this potential. This will be easy or hard depending on the hypothesis as well as practical and technical constraints (keep in mind that even hypothesis-free or hypothesis-generating studies still need decisions, such as about the type of donor or cell). The phenotypic readout may be apparent, at least theoretically, for gene studies. For instance, if the objective is to investigate the impact of rare disease-associated coding mutations in an ion channel gene, it makes sense to ascertain the properties of the channels that result and the purpose of the effector pathways that follow them. Additionally, fundamental cellular processes like dendritic outgrowth and synapse formation, which require cells to have a neural identity, can be studied with ease using iPSC-based models. However, when the molecular target of interest has an unknown function, the appropriate assay is frequently less clear; If a gene is involved in multiple molecular pathways or produces multiple functionally distinct products, this may be the case even for well-studied genes.

The absence of pathognomonic neuropathological changes in patients with psychiatric disorders, in

contrast to neurodegenerative diseases, means that there is no clear, let alone diagnostically significant, disease phenotype to model at the cellular level, making decisions regarding the phenotype(s) particularly challenging for case-control studies. On the other hand, even if the phenotype in the rarefied cell model of early neuronal development reflects a fundamental pathogenic mechanism, it is unknown whether the phenotype would be expected to reflect characteristics of illness in mature brains. Dendritic outgrowth and synaptic density have been shown to change in patient-derived iPSC neuronal cultures in a number of studies, which matches, at least superficially, the evidence for changes in neuropil and synaptic density in adults with some psychiatric conditions, particularly schizophrenia. Be that as it may, different discoveries are less obviously united to neuropathological perceptions. For instance, it is difficult to square the significant decreases in neuronal suitability saw in societies got from iPSCs from patients with bipolar turmoil with the restricted proof for changes in neuronal number in the minds of patients. In a similar vein, the absence of evidence for neuronal disarray in postmortem brain tissue contradicts the findings of disorganized migration of neural progenitor cells in schizophrenia patients' brain organoids. It is clear that some of the case-control differences that were found in iPSC systems could be temporary changes in the disease state as it develops. However, they might not accurately depict the actual group differences that are observed in vivo. As many neurotransmitters act as trophic factors during development, differences in neurotransmitter function in the mature brain may manifest as changes in in vitro migration. On the other hand, the absence of microglia and concurrent reduction in synaptic pruning in many iPSC models may confuse phenotypes related to synaptic size and/or number. Last but not least, group differences may also be false leads due, for instance, to a lack of sample size or the erratic nature of the in vitro environment [6-10].

Conclusion

The relatively immature nature of iPSC-derived neural cells is a major obstacle to accurately modeling neuropsychiatric disorders in vitro. Although organoids containing cells mapping to early postnatal development have recently been reported although gene expression and electrophysiological studies indicate that cells

within both 2D and 3D models remain broadly similar to early fetal neurons notably, the fetal-like identity of iPSC-derived neural cells may have some advantages, at least theoretically, despite being frequently cited as a limitation. Assuming that they really summarize parts of human neurodevelopment, they might give a window into processes that are generally to a great extent difficult to reach. As a result, iPSC-based models may provide a framework for investigating relationships between cause and effect for researchers studying neurodevelopmental psychiatric disorders like schizophrenia and autism.

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