Asian Journal of Psychiatry 25 (2017) 46–53

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ajp

Cellular models to study schizophrenia: A systematic review

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ARTICLE INFO

Article history:
Received 31 July 2016
Received in revised form 11 October 2016
Accepted 16 October 2016

Keywords:
Schizophrenia
Cell model
Pluripotent
Neuron
Psychosis

ABSTRACT

Background: Advancements in cellular reprogramming techniques have made it possible to directly study brain cells from patients with neuropsychiatric disorders. We have systematically reviewed the applications of induced pluripotent stem cells (IPSCs) and their neural derivatives in understanding the biological basis of schizophrenia.
Method: We searched the scientific literature published in MEDLINE with the following search strategy: (Pluripotent) AND (Schizophrenia OR Antipsychotic OR Psychosis). Studies written in English that used IPSCs derived from patients with schizophrenia were included.
Results: Out of 23 articles, which had used IPSCs from patients with schizophrenia, neurons or neural stem cells had been derived from them in a majority. Several parameters had been studied; the key cellular phenotypes identified included those of synaptic pathology, neural migration/proliferation deficits, and abnormal oxidative phosphorylation.
Conclusion: Cellular modelling using IPSCs could improve the biological understanding of schizophrenia. Emerging findings are consistent with those of other study designs (post-mortem brain expression, animal studies, genome-wide association, brain imaging). Future studies should focus on refined study designs (family-based, pharmacogenomics, gene editing) and a combination of cellular studies with deep clinical phenotyping.

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http://dx.doi.org/10.1016/j.ajp.2016.10.015
1876-2018/

1. Introduction

Schizophrenia is a common psychiatric syndrome associated with marked distress and disability, increased mortality, and a reduction in life expectancy by 15–25 years (WHO, 2001). In spite of receiving the best available treatments, at least 30–50% of patients respond poorly to pharmacotherapy. Schizophrenia is currently being reconceptualised as a neurodevelopmental disorder, influenced by genetic and epigenetic factors, and perhaps also by epigenetic dys-regulation in the brain, induced by various environmental factors acting at sequential and critical time windows during neuro-development (Serretti and Fabbri, 2013). Disease processes perhaps start long before manifestation of a clinically recognizable state, and disease-associated biological signatures are evident much ahead of actual disease. Research in this direction in the last one decade has improved our understanding of this complex disorder.

A better understanding of this complex disease requires not only careful measurement of clinical and biological parameters, but also an analysis of underlying changes in the relevant cell biology. Genetic studies have identified a number of potential cellular and molecular processes that need to be tested in the cellular context. It is impossible to obtain tissue samples from the brain (except in post mortem settings); therefore, approaches that allow the recreation of neural cell models *in vitro* are particularly valuable in investigating the effect of genetic variations on cells and tissues. Embryonic stem cells, as well as induced pluripotent stem cells (IPSCs) and subsequently differentiated neural cell types can thus be of particular value in studying the cellular and molecular changes in neuropsychiatric disease (Brennand et al., 2012). With this technology, one can now hope to understand how genetic variations and polymorphisms in candidate genes, prevalent in the affected population, disturb normal neuronal functioning predisposing them to disease. These findings could provide a better understanding of the disease process, and thereby help in devising better pharmacological treatments as well as novel biotechnological solutions for the diagnosis and treatment of schizophrenia.

Albeit being a promising area of research, the utility and validity of these IPSC based models in understanding the behaviour of a complex cell (neuron, glia, astrocytes etc.) within a more complex tissue (brain); and its translation to schizophrenia remains unclear. We have attempted to address this issue by systematically reviewing published literature on the application of such model systems in the understanding of the biology of schizophrenia.

2. Method

We searched the scientific literature published in MEDLINE with the following search strategy in the month of April 2016: (Pluripotent) AND (Schizophrenia OR Antipsychotic OR Psychosis). Studies were included if they had used IPSCs derived from patients with schizophrenia; only articles written in English were selected. A total of 112 citations were thus identified.

Articles were selected through assessment of the title and abstract (and if required, of the full text) to determine relevance. Records retrieved from the reference lists of these articles were screened for previously unidentified studies. The authors were contacted if any additional information was required. The first and second author of this study independently carried out the search. Any inconsistency was discussed and resolved. A total of 22 articles fulfilled the inclusion criteria and were included in this review. One additional publication (n = 1) was identified in July 2016 increasing the total to 23. The details of the literature search are illustrated in Fig. 1. The first and second authors extracted information from the full text reports/supplemental material independently. Authors were contacted if the methods/results of the study were unclear. Meta-analysis and funnel-plot (for publication bias) could not be performed due to the wide variations in methodologies used and multiple publications (with overlap of clinical sample) from the few laboratories that perform such experiments.

3. Results and discussion

Table 1 depicts a summary of all the published work that has used IPSCs derived from patients with schizophrenia. Although varied methods were used across studies from different laboratories, some common links could be made. Some of the replicated findings are discussed here.

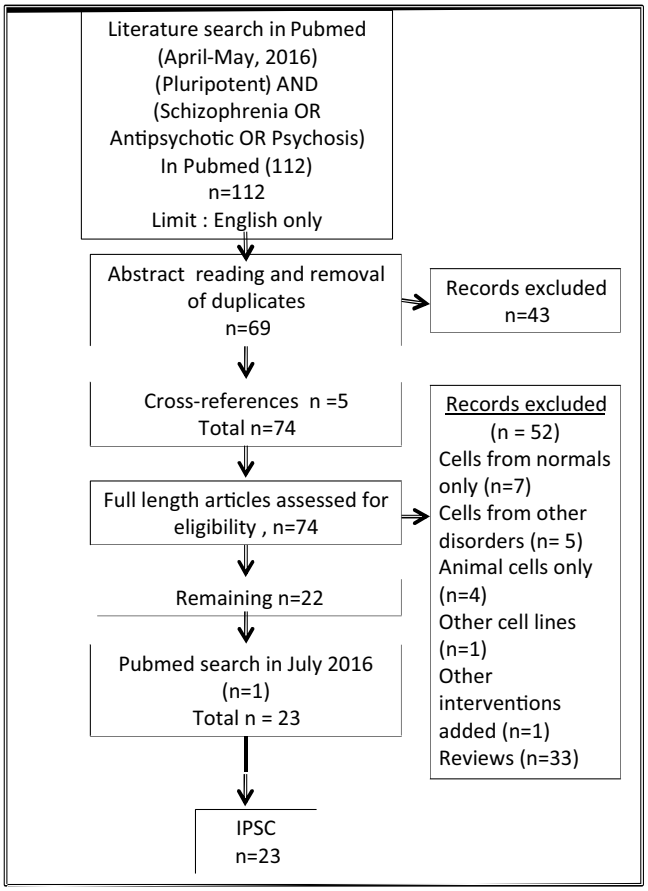

Fig. 1. Flowchart of literature search.
IPSC—Induced Pluripotent Stem Cell.