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Literature Review

Human-induced Pluripotent Stem Cell Potential for Schizophrenia Therapy: A Literature Review

Potensi *Human-induced Pluripotent Stem Cell* sebagai Terapi Skizofrenia: Sebuah Tinjauan Pustaka

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ABSTRACT

Schizophrenia is a severe and chronic mental disorder characterized by a neurodegenerative process. Currently, there has been no cure for schizophrenia. However, a newer significant potential for modeling and curing schizophrenia has been recognized in human-induced pluripotent stem cells (HiPSCs), which are obtained from adult somatic cell reprogramming. This study aimed to assess the potential of HiPSCs in schizophrenia by reviewing relevant scientific journals published in reputable databases such as Springer, Elsevier, Science Direct, Nature, and Pubmed, in the last 10 years. Research findings indicate that stem cells can help determine the effectiveness of antipsychotics and repair damaged neuronal cells in certain areas of the brain by transplanting programmed stem cells. The proliferative ability of neuronal cells in schizophrenia tends to decline, affecting their physiological neurogenesis. HiPSCs have the potential to return the neuronal function in schizophrenia, offering new hope in psychiatry.

Keywords: *Human-induced pluripotent stem cells (HiPSCs), schizophrenia, stem cells, therapy*

ABSTRAK

Skizofrenia merupakan gangguan jiwa berat dan kronis. Salah satu penyebab skizofrenia adalah proses neurodegeneratif. Hingga kini, belum ditemukan terapi yang mampu menyembuhkan skizofrenia. Dewasa ini, sel punca digunakan untuk memprogram ulang sel somatik dewasa menjadi *human-induced pluripotent stem cells* (HiPSCs) yang memiliki potensi besar dalam terapi dan model penyakit skizofrenia. Penelitian ini bertujuan untuk mengetahui potensi HiPSC dalam terapi skizofrenia dengan melakukan pencarian jurnal ilmiah melalui *database* terpercaya yaitu *Springer, Elsevier, Science Direct*, *Nature*, dan *Pubmed* menggunakan bahasa Inggris dalam 10 tahun terakhir. Penelitian menunjukan bahwa sel punca dapat membantu mengetahui efektivitas pemberian antipsikotik dan memperbaiki sel neuron yang rusak di area otak tertentu dengan transplantasi sel punca yang telah diprogram. Kemampuan proliferasi dari sel-sel neuron pasien skizofrenia cenderung menurun dan mempengaruhi fungsi fisiologisnya dalam proses neurogenesis. Penggunaan HiPSC berpotensi mengembalikan fungsi neuron pasien skizofrenia sehingga memberikan harapan baru dalam bidang psikiatri

Kata Kunci: *Human-induced pluripotent stem cell* (HiPSC), sel punca, skizofrenia, terapi

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INTRODUCTION

Schizophrenia is one of the severe and chronic mental disorders characterized by delusions, hallucinations, disorganized speech or behavior, and negative symptoms. Schizophrenia diagnosis typically requires the presence of at least two of these symptoms (1). In 2022, WHO states that approximately 24 million people worldwide (0.32%) suffer from schizophrenia. This disorder significantly impacts the functionality of the patient's life, such as occupational impairment, interpersonal relationships, or independence (2). People with schizophrenia also have a higher risk of substance abuse, displaying violent tendencies, and committing suicide compared to the general population (3).

The pathomechanism of schizophrenia involves hyperactivity of dopamine, serotonin, and glutamate receptors. Thus, the primary medications used are antipsychotic drugs that target dopamine D2 receptors, serotonin 5HT2A or 5HT1A receptors, which in reality are widely prescribed for diagnoses other than psychosis and schizophrenia due to their binding to many other receptors. This mechanism is also responsible for the side effects of antipsychotics (4). Many patients experience these side effects before achieving clinical improvement, sometimes immediately after starting therapy. Extrapyramidal effects are particularly common with first-generation antipsychotics, while low doses can induce sedation, postural hypotension, metabolic disturbances, and weight gain (5). Approximately 34% of schizophrenia patients do not achieve remission even after undergoing at least two trials of adequate doses of antipsychotics. This population continues to experience persistent negative, positive, or cognitive symptoms (6). In addition to antipsychotics, current therapeutic approaches are psychosocial therapy and electroconvulsive therapy (ECT). However, ECT is reported to reduce schizophrenia symptoms by only 30-80% with various side effects, such as tachycardia, delirium, cognitive impairment, and seizures (7).

Despite the high incidence of schizophrenia, the cellular and molecular mechanisms underlying its role remain unclear. This lack of clarity is attributed to the scarcity of available pathogenesis samples similar to schizophrenia (8). Therefore, a better treatment approach is currently being studied. One therapeutic strategy that is being widely developed is *stem cell therapy*. This approach is founded on the hypothesis that schizophrenia stems from genetic abnormalities and neurodegenerative processes within the brain.

Since their discovery by Yamanaka in 2007, stem cells have gathered significant attention. Over the past few decades, stem cells have been studied and applied in regenerative medicine. Stem cells are cells that have not specialized and have the potential to differentiate into various specific cell types that can form different body tissues (9).

Previous stem cell therapies have been employed in the treatment of certain neurodegenerative diseases including Alzheimer's and Parkinson's, primarily utilizing neural stem cells. These stem cells have been known to be able to neuroregeneration through various mechanisms, including differentiation into Schwann cells, secretion of neurotrophic factors, and facilitation of myelination (10). In Parkinson's disease, the administration of *estradiol 2 benzoate* is known to activate *integrin α5β1*, a protein expressed by striatal neurons innervated by dopaminergic neurons in the midbrain (11).

Recent discussions regarding stem cell therapy for schizophrenia have focused on the use of Human-induced Pluripotent Stem Cells (HiPSCs), where these pluripotent stem cells can be utilized for modeling schizophrenia, thereby providing a deeper understanding of the development of schizophrenia (12). The ability of stem cells to regenerate and differentiate into various types of cell types is believed to be useful as a treatment for schizophrenia in the future (13). Therefore, stem cells specific to schizophrenia have the potential for testing the new therapeutic approach, providing new insights into how each patient responds to different drug options (14).

In conclusion of this background, the newer, safer, less invasive, and more effective therapy for schizophrenia is very much needed. Therefore, further studies are encouraged. This study is aimed to review relevant scientific journals regarding the potential of human-induced pluripotent stem cells in schizophrenia. From what we know currently of the pathomechanism of schizophrenia at the cellular level, to the therapeutic potential of the HiPSCs.

METHOD

Scientific journals were searched using reliable and frequently accessed databases, including *Springer, Elsevier, Science Direct*, *Nature,* and *PubMed.* The keywords used in the literature search were “stem cell”, “schizophrenia”, and “therapy”. Subsequently, articles that matched the search keywords were filtered based on title and inclusion criteria. The inclusion criteria were full-text articles published in English within the last 10 years (2014-2024).

RESULTS

Stem cells are classified based on their differentiation potential into several categories, as follows: 1.) Totipotent: stem cells capable of differentiating into any cell type; 2.) Pluripotent: stem cells capable of differentiating into three germinal layers, except extraembryonic tissues, such as the placenta and umbilical cord; 3.) Multipotent: stem cells capable of differentiating into various cell types according to their germ line, such as *hemopoietic* stem cells; 4.) Oligopotent: stem cells capable of differentiating into several cell types, such as myeloid stem cells; 5.) Unipotent: stem cells capable of differentiating into one type of cell. Table 1 presents the sources, characteristics, and markers of these stem cells (15).

The Potential of HiPSCs in Schizophrenia

Currently, the underlying pathology of the brain in schizophrenia patients is still being studied. Recent findings suggest that abnormal myelination occurs in schizophrenic patients, which can be seen in the white matter of the brain through neurological images, such as EEG and MEG, as well as in functional MRI. This abnormal myelination can be caused by genetic and epigenetic transcriptional regulation related to calcium signal modulation. Calcium signals play a crucial role in both myelin damage (resulting from pathological calcium overload) and repair of remyelination (physiological calcium activity) (16).

Table 1. Source, characteristic, and marker of stem cells

	Source	Characteristic	Marker
Embryonic Stem Cells (ESC)	Blastocysts	• Pluripotent • Unlimited proliferation • Ethical issue • Due to the lack of complete immunocompatibility, they will likely be immune rejected • Risk of teratoma	CD133, CD31, CD59, SSEA-1. SSEA-3, SSEA-4, Oct-3/4, KLF-4, SOX2, Nanog, TRA-1-60, TRA-1-81
Adult Stem Cells (ACS)	Peripheral blood/bone marrow/adipose tissue	• Multipotent • No risk of rejection • Minimal risk of tumor formation • Limited number in tissue	Hematopoietic Stem Cells: c-Kit, CD34, Sca-1 Thy-1, CD133 Mesenchymal Stem Cells: CD90, CD105, CD73, CD44, CD117, STRO-1
Induced Pluripotent Stem Cells (iPS)	Any type of cells, the most common are fibroblast, keratinocytes, mononuclear cells of peripheral blood	• Pluripotent • Obtained through somatic cell reprogramming • Low reprogramming rate • No ethical issue • Individual regenerative medicine • Minimal risk of experiencing immune rejection • Risk of teratoma	Oct3/4, Nanog, Dax1, Ras, Zfp96

A study identified 119 calcium-dependent proteins associated with human neuropsychiatry, suggesting that modulating these calcium-dependent proteins and activity-dependent synapse plasticity could potentially rescue abnormal synapse/neuron circuits. This modulation could be complemented by stem cell therapy. Stem cells have the ability to stimulate proliferation, maturation, and myelination mechanisms in brain neural glia, particularly oligodendrocytes, in response to the cell regeneration effects of stem cells (16).

Advantages and Disadvantages of HiPSCs Therapy

Table 2. Advantages and disadvantages of HiPSCs therapy

Advantages	Disadvantages
Using HiPSCs has fewer ethical issues	The reprogramming method can cause tumorigenesis
HiPSCs reduce the chances of immune rejection in patients	HiPSCs reprogramming factors may associate with disease
Cell sources are easily accessible for reprogramming HiPSCs	The lack of quality assessment and variability makes HiPSCs unstable
HiPSCs can be used as disease models	
Reprogramming HiPSCs can reduce the overall cost of clinical trials	

Note: HiPSCs: Human-induced Pluripotent Stem Cells

The advantages and disadvantages of HiPSCs therapy are outlined in Table 2 (17). However, the safety of HiPSCs therapy remains uncertain as HiPSCs therapy has not yet been used clinically. One significant safety concern is the potential for HiPSCs to transform into malignant cells. To mitigate this risk, it is imperative to establish a HiPSC differentiation protocol to ensure the appropriateness of the cell population (18). Some of the obstacles to using HiPSCs as a therapy are the high cost and lengthy fabrication process. This situation is also limited by the unresolved transplantation problem, particularly concerning the use of integrative methods involving the oncogenic transcription factor c-Myc (19).

DISCUSSION

Stem cells are primitive cells that have the potential to differentiate into all types of specialized adult cells. Through cell division, stem cells can generate cells identical to those found in adult tissues (20). Stem cell therapy is currently being developed for schizophrenia patients, to repair nerve cell damage in the brain and potentially prevent the onset of schizophrenia. The number of studies on stem cells continues to increase every year (Figure 1) (21).

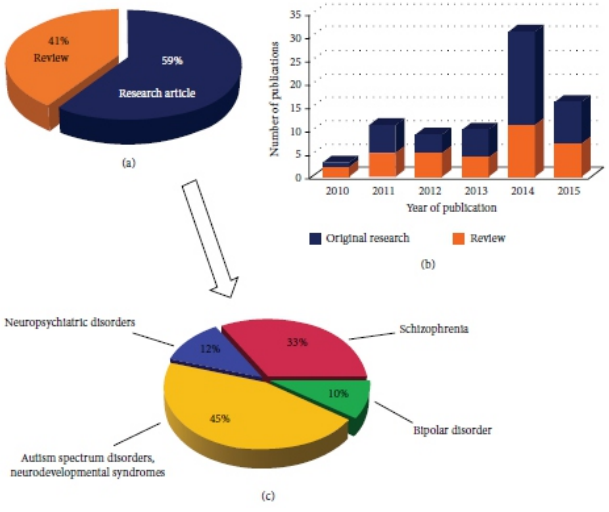

Figure 1. Number of iPSCs studies year by year (21)

The development of induced Pluripotent Stem Cell (iPSC) technology has created new possibilities for studying psychiatric diseases. Studies have shown that antipsychotic treatments, such as the dopaminergic antagonist loxapine (but not risperidone, olanzapine, and clozapine), for three weeks can improve neural connectivity in HiPSC model-derived neurons (22).

Nowadays, HiPSC technology has been utilized in the mouse brain through transplanting its derivative cells (23). Similarly, HiPSCs have been employed in experiments involving the nervous system, differentiating into neuron cells and glia cells within eight weeks in experimental rats with spinal cord injuries (24). Furthermore, the use of HiPSCs as a therapy for central nervous system disorders, such as stroke, traumatic brain injury, spinal cord injury, and Parkinson's, has recently been reviewed. HiPSCs can be used as a resource for *in vitro* disease modeling and as a model for therapeutic options for disorders in psychiatry (24,25).

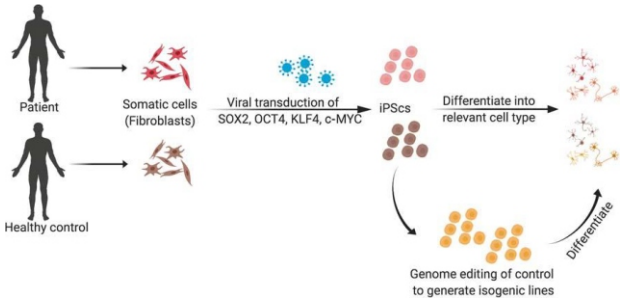

Figure 2. Modeling neuropsychiatric disorders using iPSCs (25)

The latest treatment for schizophrenia using HiPSCs is currently underway (26). Among the types of stem cells potentially applicable to schizophrenia therapy are neural stem cells (NSCs). NSCs, sourced from embryonic or fetal stem cells, umbilical cord blood, or mesenchymal or ectodermal stem cells, constitute a heterogeneous population capable of self-repair and regeneration under specific microenvironmental stimuli. NSCs have been observed in particular areas of the brain, including the ventricular or subventricular zone, the subgranular zone, and the subcallosal zone, indicating their status as instances of ongoing cell generation in adulthood (27).

Disease modeling of HiPSCs can be performed *in vitro* using various technologies, cell stages, cell types, patient samples, and analytical methods (Figure 4). Precisely corrected iPSCs (depicted in blue) can be generated from known genetically aberrated iPSCs (depicted in red) using CRISPR-Cas9 technology. Specific genes from healthy iPSCs (depicted in green) can be selected to generate isogenic *knock-out* iPSC lines. This then provides the information for investigating the role of genetic variation in neurogenesis. All iPSC lines can be analyzed through differentiation in monolayer or 3D cerebral organoid generation. Phenotype changes during iPSC differentiation can be observed. In the context of schizophrenia, comparisons can be made between patient-derived iPSCs or iPSC knockouts and healthy control iPSCs or corrected iPSCs, with each cellular process noted above. The effects of other factors such as environmental stressors during differentiation procedures should be considered (8).

The reprogramming technology of iPSCs, especially in neurodevelopmental disorders, has recently acquired significant research attention focused on understanding pathogenesis and etiology. This has led to the emergence of a new therapeutic approach at the cellular level, termed “pharmacy-iPSCellomics”. Discoveries at the cellular level are enhancing understanding of neurodevelopmental disorders better, resulting in changes in comprehension of how new antipsychotic treatments function. Ex vivo drug testing at the cellular level is used to assess the safety of the treatment and the side effects of treatment prior to human trials. Several drug treatments that have gone through the ex vivo testing stage and subsequent human trials have been approved by the FDA. As more patients require therapy using this technology, the practical application of iPSCs technology will become more apparent (28).

While the discovery of stem cells offers new hope for schizophrenia treatment, there are significant challanges that must be addressed. One prominent limitation is the issue of small sample sizes, with many studies in this area involving fewer than five samples, increasing the risk of false positive outcomes. Transplantation has been tested in mice but has yet to be applied to humans. Additionally, there are

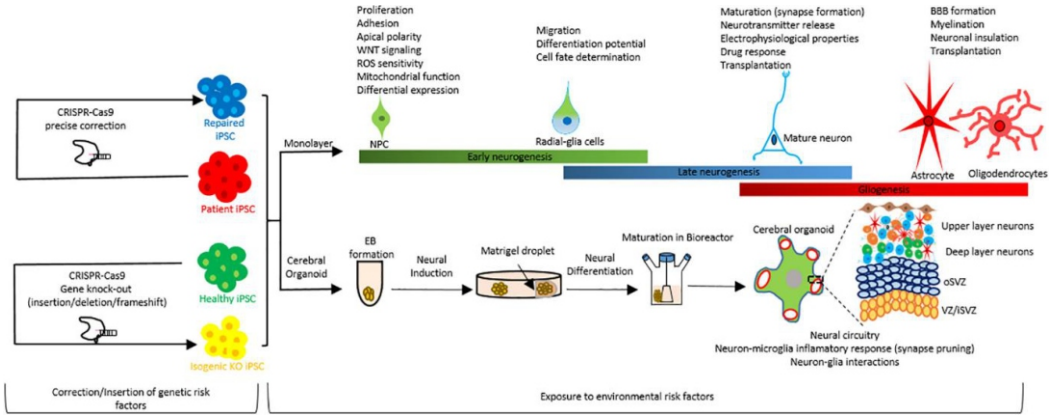

Figure 3. Using iPSC technology to model schizophrenia in vitro (8)

also several other limitations of using stem cells for schizophrenia therapy, such as the risk of immunologic rejection, tumorigenicity, and surgical and infectious risks. Further studies are required to overcome issues related to donor samples, regulating ethical considerations of donor sources, development procedures, and expert authorization.

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