

The Future of Mental Health Care: Use of Induced-Pluripotent Stem Cells for Characterization, Diagnosis, and Treatment of Bipolar Disorder

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Abstract

The need for an effective and accurate tool to diagnose and treat mental disorders, like bipolar disorder, can be solved using induced pluripotent stem cells. Through the reprogramming of somatic cells, one can create a patient-specific in vitro model to study the cellular and molecular pathways occurring in vivo. By studying and understanding the levels of specific proteins associated with different disorders, one could characterize, properly diagnose, and provide an effective treatment for a patient without risking a misdiagnosis often associated with verbal presentation of symptoms. Induced pluripotent stem cells also provide a model to study drug responsiveness and determine if a patient is resistant to a specific treatment rather than using a trial-and-error method with prescriptions. The use of these cells will decrease the number of misdiagnosed patients and ensure that a patient is receiving a treatment that is effective for their specific case. More research is needed before the use of pluripotent stem cells is mainstream but they provide a promising path for the future of mental health care.

Keywords

Bipolar disorder; Induced pluripotent stem cells, neuronal differentiation, personalized medicine, lithium

Introduction

Mental health care, to some extent, is already tailored to the patient's specific case; the doctor considers the symptoms the patient presents with, their family history, etc. to make the diagnosis based on known illnesses that mirror the situation presented. Unfortunately, many patients with bipolar disorder (BD) seek help during a depressive episode which results in the misdiagnosis of unipolar depression [1,2]. The National Depressive and Manic-Depressive Association (DMDA) found that 69% of patients with BD were initially misdiagnosed— some receiving three to four misdiagnoses and 31% being misdiagnosed for 10 or more years [1,2]. Common misdiagnoses include 60% being diagnosed with unipolar depression, 26% with anxiety disorder, 18% with schizophrenia, and 17% with borderline or antisocial personality disorder [2]. Studies have varied in results but most have found that, on average, it takes a patient 5-7 years before they are properly diagnosed and 48% of patients have seen three or more mental health professionals before the correct diagnosis was made [1,3]. The economic burden of inadequately treated BD— from misdiagnosis and inappropriate treatment— results from increased treatment cost to receive a proper diagnosis, increased suicide risk, and increased likelihood to miss work or not perform to full function during a misdiagnosis [1,4]. A patient-specific cellular-based model is needed to characterize, diagnose, and determine a treatment plan specific to the patient's case— induced pluripotent stem cells (iPSCs) are the solution to this need.

Stem cells provide an abundance of potential in all fields of medicine on account of their unique ability to divide and differentiate into multiple cell lineage pathways. Reprogramming technology has created the ability to modify some adult somatic cells into iPSCs which closely mirror embryonic stem (ES) cells in their ability to differentiate and grow indefinitely [5]. Since the isolation of a patient's central nervous system (CNS) cells is not viable, induced differentiation of stem cells is required to obtain an accurate in vitro understanding of the cellular processes occurring in vivo. Neurons and glia, as well as cells of other CNS lineages, can be differentiated from iPSCs and these cell models allow for observation of patient-specific characterization [6]. Specifically, iPSCs allow for in vitro observation of a patient's neural and glial interactions allowing for a more personalized diagnosis based on cellular signaling and other characteristics rather than a symptomatic based diagnosis. iPSCs have proven to be a powerful tool to study and determine genetic risk factors related to BD and the effects they have on cellular and molecular signaling [7]. Studies have shown that iPSCs derived from a patient with BD have distinct alterations in neuronal excitability, neural patterning, and postmitotic calcium signaling all of which have been observed to respond to treatment with lithium, the drug of choice for treatment of BD [7]. In this review, we aim to focus on the utilization of iPSCs as a tool to model disorders in vitro, properly

diagnosis patients, and provide the best treatment for the patient from the start.

Bipolar Disorder

BD is a complex and chronic mental disorder and worldwide is among the most debilitating chronic illnesses a person can have [8]. The prevalence of BD is approximately 1.4% to 1.6% worldwide and it is associated with a 20 times increase in the risk of suicide when compared to the general population [1]. The mental disorder results in unusual shifts in energy, concentration, activity level, mood, and ability to perform daily tasks [9]. There are two subcategories within the diagnosis: Bipolar I Disorder (BDI) and Bipolar II Disorder (BDII) [9]. The major distinction between the two is the presence of either mania or hypomania for BDI and BDII respectively [9,10]. In general Bipolar II has been considered the “mild” form of Bipolar I, but recent studies have shown that although Bipolar II patients do not experience the symptoms of intense mania, the disorder is associated with more frequent episodes showing that it is still a severe impairment [10,11]. BDI is found to have higher rates of hospitalization, usually due to manic episodes that require inpatient care, and the use of mood stabilizers and antipsychotic drugs, psychoeducation, and electroconvulsive therapy are more common methods of treatment [10]. In contrast, BDII is found to have a greater risk of suicide due to more frequent depressive episodes and higher comorbidity with other psychiatric conditions like eating, personality, and anxiety disorders as well as attention deficit hyperactivity disorder (ADHD) [10]. Patients with BDII are generally younger at the onset of symptoms and are known to have a family history of the disorder [10]. Interestingly, BDII patients have been shown to have better psychosocial functioning including self-sustainability, higher education, ordinary housing conditions, and families [10]. Treatments for BDII generally include antidepressants and lamotrigine in combination with psychotherapy [10]. As stated previously, the most common misdiagnosis for BD is unipolar depression, or major depressive disorder (MDD).

When diagnosed, many patients then begin taking antidepressants to alleviate symptoms, but without the combination of a mood stabilizer, the medication can induce a manic episode and result in the triggering of rapid cycling [1,3,12]. Rapid cycling is defined as the presence of four or more mood episodes, varying from manic to depressive, that occur in the span of 12 months [13]. Antidepressant-induced rapid cycling is found to be more common in females, shows comorbidity with an ADHD diagnosis, and is seen more frequently in BDII patients [3,11,12,14]. Although it does not affect every patient, it is extremely debilitating to those who do experience it. The rate of misdiagnosis can be attributed in part to high comorbidity with other medical diagnoses which includes alcohol and drug abuse, panic disorder, obsessive compulsive disorder, social phobia, ADHD, personality disorders or medical conditions like multiple sclerosis or thyroid disease [1].

Induced Pluripotent Stem Cells

Adult somatic cells can be induced into an embryonic-like state through reprogramming by the transfer of nuclear contents [15]. This is done by the ectopic expression of transcription factors OCT3/4, Sox2, c-Myc, and Klf4, which are able to induce somatic cells to pluripotency, hence the name induced pluripotent stem cells [5,15]. Most publications utilize Yamanaka’s retroviral method [15] of

induction due to higher efficiency but his model risks transgene reactivation and insertional mutagenesis that can be avoided using non-integrating methods [5]. Non-integrating methods rely on plasmids and Sendai viruses or use of synthetic mRNAs and small molecules, both of which are viable methods that may eventually become the mainstream method of reprogramming [5]. iPSCs can be used to study the phenotypes of monogenic diseases and late-onset polygenic diseases and genetic differences seen in iPSCs can be traced back to the somatic cell of origin [15].

These cells have the ability to differentiate into multiple CNS lineages allowing for an in vitro characterization of cellular phenotypes that are specific to the patient— providing disease-specific and patient-specific cell models to allow for easier diagnosis [6]. Setbacks in interpreting data from studies occur due to incomplete reprogramming and lab-to-lab variability [16]. A standardize, safe, and efficient method of reprogramming needs to be determined before widespread use of iPSCs can be utilized.

Neurodevelopmental origins of BD

It is estimated that the heritability of BD is about 85-95%, with twin, family, and adoption studies supporting this evidence [16,17]. Despite this genetic link, there is no clear event or pathway that explains the hereditary component of the disorder. There is however strong evidence that supports neurodevelopmental origins of BD. Altered pathways related to cell migration, calcium signaling, nervous system development, H3K4 methylation, and the extracellular matrix have all been associated with BP through genome-wide association studies (GWAS) [16]. As well as differences in calcium signaling and activity, blocks or delays in neuronal differentiation, and changes in both neuronal and glial lineage specification [16,18].

Alterations in signaling in the Wnt, hedgehog, and Nodal pathways have been linked to impairment of differentiations of BP patient-derived neurons to dorsal telencephalic derivatives [6,16]. GWAS has shown that mutations within the DISC1 gene have been linked to various mental illnesses including BD; DISC1 is known to regulate neural progenitor proliferation by inhibiting glycogen synthase kinase 3 β — a target for lithium signaling [6]. These discoveries have shifted the focus of study of BD from neurodegenerative origins to a neurodevelopmental one. Studies using RNA-Seq on iPSCs from BD patients have shown changes in expression of long non-coding RNAs, coding genes, splice isoforms, and pseudogenes when compared to healthy controls during differentiation to neurons [19]. iPSCs have also been used to show that an increase in microRNA (miRNA), specifically miR-34a expression, is linked to impairments in neural cell differentiation and neuronal morphology and decreases in expression of synaptic proteins, while the reduction of miR-34a results in enhanced dendritic elaboration [20]. In a study comparing iPSC lines from unaffected parents and their two BDI-diagnosed children, it was observed that there was [16]:

- Increased expression of CNTN6, SCN2A, SYN1 for BDI.
- Increased expression of IRX2, MAP2, NEFM, SOX2, NRCAM, MSI2 after differentiation for BDI.

- Higher levels of DISC1, PAX6, DCX, and NKX6-1 in control NPCs.
- Increased expression of ASCL1, ATOH1, POTES, TFAP2A, CACNA1E, CTIP2, HEY1, MSX1, RELN, KLF4, CACNA1G and GFAP in control neurons after differentiation.

If replicated results concluded the same cellular differences, these observations could be used as criteria for the minimum cellular and molecular abnormalities that constitute a patient having BDI. These markers would need to be unique to BDI and therefore differ from the criteria determining BDII and any other mental illness, although some overlap may be inevitable.

Lithium as an Effective Treatment Option: a model shown by iPSCs

Lithium is the first-line of treatment for patients newly diagnosed with BD and has been the drug of choice for nearly 70 years [21]. It aims to treat acute episodes and prevent relapses, targeting both the manic and depressive episodes associated with BD [21]. Lithium treatments have shown to help increase the rate of brain serotonin synthesis by up to 80% and brain tryptophan by 70% [22]. A patient must actively take lithium throughout their life to experience its benefits as discontinuation has resulted in the recurrence of symptoms [23]. Without treatment it is estimated that approximately 15% of patients commit suicide, making the proper diagnosis and treatment plan crucial to recovery [24]. A study observed that lithium treatment selectively reversed the hyperactive Ca^{2+} action-potential firing in select iPSC from patients with BD. This observation was strictly observed in cell lines from lithium responsive patients and was not observed in lithium resistant patients [24]. This concept opens the idea that one could test if patient-derived iPSCs were responsive to lithium, or other drugs, before prescribing the treatment therefore avoiding any adverse side-effects from ineffective drugs. One method that has shown to be effective in determining drug response in iPSCs is the use of label-free imaging assays to determine if there is an optical measure of cell adhesion which directly correlates with clinical response to lithium treatment— i.e., treatment of the patient with lithium will be effective [25]. Interestingly, lithium has also been shown to enhance the generation of iPSCs in vitro, improving the efficiency by which the cells are reprogrammed [26].

Conclusion

Let me paint a picture of the future of psychiatry as written by this review: a patient presents with the following symptoms that have been persistent for about two weeks— extreme sadness, loss of interest in work and loss of pleasure in hobbies, decreased energy, and suicidal ideation [27]. After further questioning on past health and family history the most viable diagnosis is MDD (unipolar depression). Rather than immediately starting the patient on antidepressants— which can result in rapid cycling for those with BD that are misdiagnosed— somatic cells are extracted, reprogrammed into iPSCs, and differentiated into cells of CNS origin. The cellular and molecular pathways of these cells are studied and any distinct differences from control cells are recorded. These observations are then compared to phenotypes exhibited by cells of known origin and illness including major depression, BD, schizophrenia, etc. After comparison it becomes apparent that the patient has BD and not major

depressive disorder. The first treatment plan is lithium but after further tests with the patient's specific cell lines, it is seen that their cells are lithium resistant, and an alternate course of action needs to be taken. The use of iPSCs not only saved the patient from years of misdiagnosis, and possible induction into rapid cycling, but it also allowed for a more viable treatment plan to be created since it was found that their cells were lithium resistant.

Although the initial cost and time it will take to treat each patient using this method may seem unreasonable, looking long term will show how taking the time to utilize resources to properly diagnose and treat a patient will ultimately be more cost effective by significantly lowering the rate of misdiagnosis and mistreatment therefore lowering suicide rate and allowing people to return to their full functional ability. Much research is still needed before this becomes a viable and wide-spread option for practical use. First, more research is needed to come to a consensus on the most efficient and viable way to reprogram somatic cells and differentiate iPSCs to cells of CNS origin— this method must be universal and easily replicable. Second, the abnormal genotypic changes, as well as phenotypic results due to those changes, need to be studied, compared to control cells, and recorded. A consensus needs to be met for the minimum cellular and molecular abnormalities that constitute a specific illness— e.g., changes in postmitotic calcium signaling directly correlate with BD; if this is seen in a model (along with other key criteria) the patient is diagnosed with BD. Finally, a standardized method is needed to test treatment plans once a patient is accurately diagnosed— i.e., this will be a standardized method the psychiatrist will use to determine if a BD- patient is lithium resistant. iPSCs provide an exciting and promising future for the next step in personalized mental health care.

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