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Potential Use of Stem Cells in Mood Disorders

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Abstract

Mood disorders are heterogeneous conditions characterized by complex genetics, unclear pathophysiology, and variable symptomatology. Currently, there is no biomarker for the diagnosis or prognosis of mood disorders, and the treatments are of limited efficacy in a significant proportion of patients. Furthermore, the disease models are not able to recapitulate their complexity. In this scenario, stem cells may have different applications in mood disorders. Circulating stem cells may be regarded as potential biomarkers. Mesenchymal stem cells are a promising therapeutic strategy for mood disorders as they promote neurogenesis and increase the expression of neurotrophic factors that enhance the survival and differentiation of neurons. In addition, induced pluripotent stem cells, cells reprogrammed from somatic cells of healthy subjects or patients, offer a great opportunity to recapitulate both normal and pathological development of human brain tissues, thereby opening a new avenue for disease modeling and drug development in a more disease-relevant system.

Keywords

Bipolar disorder · iPSCs · Major depressive disorder · Mood disorder · MSCs · Stem cells

1 Introduction

Mood disorders, specifically, major depressive disorder (MDD) and bipolar disorder (BD), encompass a constellation of symptoms involving emotional, cognitive, and behavioral domains. Mood disorders are highly prevalent worldwide, being recognized by the World Health Organization (WHO) as a major source of morbidity and mortality (Kessler et al. 2006; WHO 2012). These conditions are frequently chronic and debilitating (Whiteford et al. 2013; Marotta et al. 2015). Patients with mood disorder are also at higher risk for developing a wide range of medical conditions, including cardiovascular and cerebrovascular diseases, and metabolic syndrome (Cizza 2011; Goldstein et al. 2015).

The pathophysiology of MDD and BD is still unclear. Family studies have provided consistent evidence that genetic factors are implicated in

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their pathogenesis (York et al. 2005; Kendler et al. 2011). Environmental factors influencing pre- and post-natal development have also been associated with mood disorders (Pedersen et al. 2017). In addition, patients with mood disorders present changes in several brain structures (Strakowski et al. 2002; Lyoo et al. 2006; Wise et al. 2016), peripheral levels of inflammatory, oxidative stress and neurotrophic biomarkers (Pfaffenseller et al. 2013; Sayana et al. 2017; de Melo et al. 2017; Castren and Kojima 2017).

Although a reasonable number of therapeutic options exist for MDD and BD, their treatment is still challenging. Treatment response is variable and difficult to predict from the beginning. Treatment resistance is not uncommon, especially for those patients with depressive episodes. There is a critical need to identify more effective therapeutic strategies for mood disorders

by targeting receptors and/or signaling pathways beyond the monoamine systems (Papakostas and Ionescu 2015; Colpo et al. 2017). Taking into account the heterogeneous and complex neurobiology and clinical presentation of mood disorders, it is important to develop treatments that modulate specific pathophysiological processes. For exam-ple, immune-based strategies should be used for inflammation-related depressive and bipolar illnesses, while circuit modulation for those with identified brain circuitry dysfunctions (Colpo et al. 2017; Riva-Posse et al. 2017).

Despite the great effort and resources invested in research for drug discovery and novel therapeutics, the drug attrition rate remains very high in psychiatry, and only a small percentage of new drugs enter the market (Waring et al. 2015). Accordingly, there is a growing clinical interest in the use of stem cells as therapy, especially for patients resistant to conventional treatments. The objective of the current review is to summarize the potential use of stem cells in mood disorders, highlighting their role as biomarkers, as a new therapy for mood disorders, and as a model for these psychiatric disorders (Fig. 1).

2 Circulating Stem Cells in Mood Disorder Patients

Under physiological conditions, low number of stem cell populations, including hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), endothelial progenitor cells (EPCs), as well as very small embryonic-like stem cells (VSELs) can be detected in the peripheral blood (Borkowska et al. 2014; Borkowska et al. 2016). These number can increase during stress or in response to tissue damage (e.g., heart infarct, stroke, intestinal inflammation, or skin burns) (Ratajczak et al. 2011). The release pattern of these cells into the blood differs according to the condition, therefore, they may be regarded as potential biomarkers.

Previous studies investigated the profile of circulating EPCs in different diseases. There are reduced numbers and/or impaired function of EPCs in cardiovascular diseases, diabetes mellitus and hypertension (Loomans et al. 2005). Some studies have also investigated EPCs in patients with depression, mostly in the context of cardiovascular diseases. They found that patients with cardiovascular diseases and depression present significantly lower levels of circulating EPCs compared with patients with the same cardiovascular problem but without depression (Di Stefano et al. 2014; Felice et al. 2015; Chen et al. 2013).

In 2009, Dome et al. was the first group to describe a decreased number of EPCs in patients with major depression (without medical comorbidity) when compared with healthy subjects (Dome et al. 2009). In 2011, Yang et al. confirmed these results, showing that depression was associated with lower levels of circulating EPCs (Yang et al. 2011). In a subsequent study, Dome et al. did not find any difference in the number of EPCs between baseline and after effective antidepressant treatment in patients with major depression (Dome et al. 2012). As EPCs are involved in vascular integrity (Khakoo and Finkel 2005), these results might suggest that

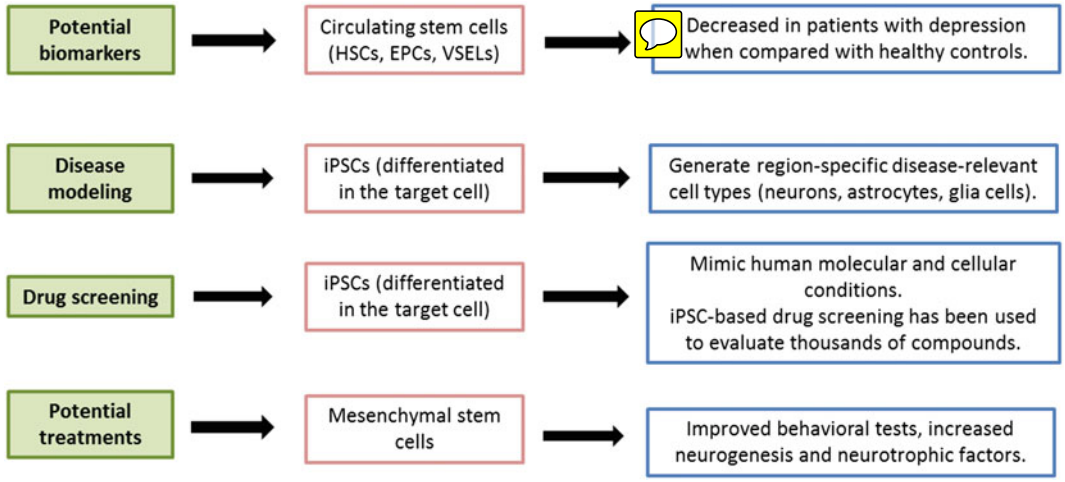

Fig. 1 Potential use of stem cells in mood disorders

mood disorders could contribute to the development of endothelial dysfunction and atherosclerosis. Interestingly, epidemiological studies show that patients with mood disorder are at increased risk of incident atherosclerosis and cardiovascular diseases (Baune et al. 2006).

In BD, there is only one study that investigated the effect of lithium treatment on circulating stem cells in the peripheral blood. In BD subjects not taking lithium, the number of VSELs, MSCs and EPCs was significantly higher than in control subjects. In lithium-treated patients, these values were similar to controls and the number of VSELs correlated negatively with the duration of lithium treatment and serum levels of lithium (Ferensztajn-Rochowiak et al. 2017). These results suggest that treatment with lithium can reduce the number of circulating VSELs, and VSELs may be regarded as a potential biological marker of the illness and its clinical progression.

3 iPSCs as a Tool for Disease Modeling

The identification of better therapeutics for mood disorders has been challenging, and very few effective strategies have been developed in the last decade. Identifying the pathological mechanisms underlying human diseases plays a key role in discovering novel therapeutic strategies. The incomplete understanding of the human brain and the complex genetic basis of mood disorders are some of the obstacles that hinder the progression of research in this area. Another major obstacle is the lack of a valid preclinical model that recapitulates all the aspects of the human disease, especially the different mood polarities of BD. Despite that, animal models have contributed to the understanding of the roles of specific genes, molecular and cellular signaling pathways in mood disorders (Slattery and Cryan 2014). Post-mortem brain tissue is an alternative for studying mood disorders, but it only provides an end-stage picture of long-standing changes in the brain structure at both cellular and molecular levels.

In the last years, the research in pathophysiological basis of diseases has been revamped by the emergence of cellular reprogramming technologies which can turn differentiated somatic cells into induced pluripotent stem cells (iPSCs) by inducing the expression of key transcription factors that define the embryonic stem cell state (Takahashi and Yamanaka 2006; Takahashi et al. 2007; Kunisato et al. 2011). iPSCs have been generated from patients' fibroblasts, keratinocytes, hair follicles, peripheral blood and likely most other cell types (Soliman et al. 2017).

One of the greatest advantages of the iPSC technology for modeling human diseases is that iPSCs contain the entire genetic background of the donor, making the technology particularly suitable for addressing diseases with defined genetic causes. In this sense, these cells are ideally suited to identify alterations in cell behavior, distinguish the affected cell type(s), examine gene expression and identify and test novel signaling pathways. However, epigenetic changes are lost during the reprogramming process. For conditions like mood disorders, in which environmental factors play a major role in epigenetic modifications, this may be of great concern (Soliman et al. 2017). Another challenge in disease modeling with iPSC technology is to generate region-specific disease-relevant cell types. There is an enormous diversity of cell subtypes in the central nervous system, and different psychiatric disorders can target distinct subset of neurons. In order to model their pathogenesis with iPSC technology, it will be necessary to generate the specific neuronal cells targeted by the mood disorders. Due to the complex nature of mood symptoms, involving multiple affective, cognitive and behavioral domains, different subtypes of neuronal cells and glial cells, or even neural circuits, must be take into account for meaningful *in vitro* modeling (Hansen et al. 2011).

A group of researchers created iPSCs from the fibroblasts of patients with BD, and these iPSC model neurons were hyperexcitable, firing action potentials at a higher frequency than control neurons. Accordingly, these neurons showed altered expression of calcium signaling and mitochondrial genes (Mertens et al. 2015). Importantly, this hyperexcitability exhibited by hippocampal neurons was selectively reversed by lithium treatment only in neurons derived from patients who also responded to lithium treatment, but not by neurons derived from non-lithium responders.

Two independent groups proposed protocols for generating serotonergic neurons from iPSC cells. Xu et al. reported that human primary fibroblasts were directly converted to induced-serotonergic (i5HT) neurons by the expression of Ascl1, Foxa2, Lmx1b and FEV. They observed that i5HT neurons expressing markers for mature serotonergic neurons had Ca2 + −dependent serotonin release and selective serotonin uptake, and exhibited spontaneous action potentials and spontaneous excitatory postsynaptic currents (Xu et al. 2016). Vadodaria et al. showed that overexpressing the transcription factors NKX2.2, FEV, GATA2 and LMX1B in combination with ASCL1 (Achaete-scute homolog 1) and NGN2 (Neurogenin-2) directly and efficiently generated serotonergic neurons from human fibroblasts. Induced serotonergic neurons showed increased expression of specific serotonergic genes known to be expressed in raphe nuclei. These neurons displayed spontaneous action potentials, releasing serotonin *in vitro* and functionally responding to selective serotonin reuptake inhibitors (SSRIs) (Vadodaria et al. 2016). Serotonergic neurons are dysregulated in depression and are the target of commonly used antidepressants such as the SSRIs. These new methods may help the study of serotonergic neurons from patients, possibly contributing to a deeper understanding of the pathways involved in the phenotypic heterogeneity of mood disorders.

4 iPSCs for Drug Screening for Mood Disorders

Traditional high-throughput screenings for drug use either immortalized cell lines or rodent primary cells which have questionable validity either from artifacts of overexpression or by virtue of simply being nonhuman with poor track records for predicting results of potential therapeutics in clinical trials (Eglen and Reisine 2011; McGonigle and Ruggeri 2014).

The use of iPSCs has become a valuable tool for drug screening due to its specific advantages as a model more tailored to faithfully mimic

human molecular and cellular conditions. iPSCs are a valuable source of primary cells with relatively stable genomes that can be cultured, expanded and differentiated to model different tissue-systems. Also, its intrinsic ability to self-renew allows for scaling up stem cell colonies for high throughput assays and drug screening purposes. However, there are some limitations. The confirmation of the link between genotype and disease can be misleading due to the complexity of the individual's genetic composition and the potential influence of epigenetic changes on disease manifestation. These limitations can increase exponentially when studying complex disorders as mood disorders in which multiple genes and environmental factors seem to play a pathogenic role.

Overall, iPSC-based drug screening has been used to evaluate thousands of compounds for several diseases (Burkhardt et al. 2013; Corti et al. 2015), and some candidates have been identified (Bright et al. 2015; Naryshkin et al. 2014; Mullard 2015). So far no study using iPSCs for drug screening for mood disorder was published. This reflects at least in part the complexity and heterogeneity of these disorders.

Another application of disease-specific iPSCs is in drug repurposing, in which existing drugs already approved for specific diseases are tested to find new applications in other diseases. For example, the anti-epileptic drug ezogabine demonstrated efficacy in an iPSC model of amyotrophic lateral sclerosis and is now undergoing clinical evaluation for this latter indication (McNeish et al. 2015).

Although a great progress has been made with iPSCs technology and drug discovery platforms, there are still several challenges that need to be addressed. First, cell-type heterogeneity reduces the chances of identifying a positive hit, illustrating the need for better differentiation protocols. Second, the culture conditions need to be controlled and standardized. Third, phenotypic assays need to be robust and should be disease-relevant. Finally, animal models are still required for the validation of positive hits from iPSC-based screening platforms. Despite these challenges, this technology holds great promise as a new translational platform for drug testing using human neurons.

5 Stem Cells as an Alternative for Treatment Resistant Patients with Mood Disorders

Mesenchymal stem cells (MSCs) are possibly the best example of stem cells with potential therapeutic implication for mood disorders. MSCs are multipotent progenitor cells that have the capacity to differentiating into all lineages of mesodermal origin, e.g. cartilage, bone, and adipocytes (Pittenger et al. 1999). Studies have shown that MSCs are also able to differentiate into cells from sources other than the mesoderm, such as neurons and hepatocytes (Dezawa et al. 2004; Hermann et al. 2004).

Clinical interest in the use of MSCs has increased significantly in the last years as they present ideal characteristics for regenerative medicine such as plasticity and high self-renewal capacity. In addition, MSCs are known for their ability to promote the neurogenesis of primary neural progenitors and survival of neural cells by expressing soluble factors, including brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) and insulin-like growth factor-1 (IGF-1) (Crigler et al. 2006). As a result of their immunomodulatory properties, they can also prevent apoptosis and decrease inflammatory responses (Crigler et al. 2006; Yoo et al. 2008). Besides soluble factors, MSCs release membrane-derived extracellular microvesicles (ExMVs) that can deliver mRNA, miRNA, and functional proteins to target cells, thereby additionally promoting cell survival and proliferation (Ratajczak et al. 2016; Ratajczak and Ratajczak 2016, 2017). All these paracrine effects mediated by soluble factors and/or ExMVs seem to be the main factors responsible for the positive results observed in patients after systemic or local stem cell therapies (Ratajczak et al. 2016; Ratajczak and Ratajczak 2016).

Based on the evidence that mood disorders are associated with a low-grade inflammation and a reduced neurotrophic support (van den Ameele

et al. 2017; Zhang et al. 2016), MSCs may be a promising therapeutic strategy for those conditions. However, only a few studies have evaluated the effects of MSC in pre-clinical models of mood disorders.

Tfilin et al. showed that the intracerebroventricular administration of MSCs improved depressive-like behavior and increased hippocampal neurogenesis in a genetic animal model of depression (Flinders sensitive line, FSL rats). The increase in hippocampal neurogenesis suggests that this can be the antidepressant mechanism of MSCs transplantation in the rat brain (Tfilin et al. 2010). These results confirmed prior studies showing increased neurogenesis after implantation of human MSCs into the dentate gyrus of mice and after transplantation of neural progenitors into the hippocampus of prenatally heroin-exposed mice (Munoz et al. 2005; Ben-Shaanan et al. 2008). More recently, Shwartz et al. also treated FSL rats with intracerebroventricular MSCs. They showed that MSCs administration attenuated depressive-like behaviors as assessed by the forced swim test, novelty exploration test and sucrose self-administration paradigm (Shwartz et al. 2017). Conversely, another study showed that intra-hippocampal transplantation of MSC enhanced neurogenesis in wild-type rats. In order to examine the behavioral consequences of intrahippocampal MSC transplantation in the rats, they assessed locomotion, learning and memory, and anxiety-like and depression-like behavior, but they did not observe any behavioral change (Coquery et al. 2012).

To the best of our knowledge, no stem cell therapies have been performed in patients with mood disorders. Based on the promising results from studies with MSCs in patients with multiple sclerosis, amyotrophic lateral sclerosis (Llufriu et al. 2014; Connick et al. 2012; Karussis et al. 2010; Sykova et al. 2017) and Parkinson's disease (Venkataramana et al. 2010; Canesi et al. 2016), conditions marked by significant mood symptoms (Kummer and Teixeira 2009), the investigation of the therapeutic potential of MSC for mood disorders is definitely warranted.

There are significant challenges to treat these patients with stem cells. First, it is important to decide which the patients are eligible for receiving the MSCs (e.g. refractory to conventional treatments). Another challenge refers to the schedule of administration of autologous stem cells to maintain clinical improvement, i.e. whether single or repetitive doses are necessary for remission.

6 Conclusion

The understanding of the pathophysiology and the development of new therapies for mood disorders have been a great challenge in psychiatry. The heterogeneity and complexity of these disorders along with the lack of valid and reliable biomarkers have hampered the advance of the field.

Stem cells have already influenced several areas of medicine. Stem cells as therapy have been used to treat human diseases such as metabolic, cardiovascular and neurodegenerative diseases. Regarding mood disorders, stem cells have only been used in pre-clinical studies. Based in the results obtained in other areas, especially neurodegenerative diseases, stem cells seem to be promising, especially for treatment-resistant patients with mood disorders.

iPSCs can reveal new relationships between disease phenotypes and gene expression profiles, which have broadened and deepened the understanding of different diseases. However, investigating mood disorders that are seemingly caused by multiple genes and/or have multiple phenotypes remains a challenge for iPSC models. With further advancement in stem cell technology, iPSCs will probably contribute to the refinement of mood disorder pathophysiology.

Conflicts of Interest The authors declare that they have no conflict of interest.

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