Progress in Neuropsychopharmacology & Biological Psychiatry 80 (2018) 23–27

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

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

Adult stem cells in psychiatric disorders – New discoveries in peripheral blood

Jolanta Kucharska-Mazur[a], Marcin Jabłoński[a], Błażej Misiak[b], Dorota Frydecka[c], Janusz Rybakowski[d], Mariusz Z. Ratajczak[e], Jerzy Samochowiec[a,*]

[a] Department of Psychiatry, Pomeranian University of Medicine, Broniewskiego 26, 71-460 Szczecin, Poland
[b] Department of Genetics, Wroclaw Medical University, Marcinkowskiego 1, 50-368 Wrocław, Poland
[c] Department of Psychiatry, Wroclaw Medical University, Pasteur 10, 50-367 Wroclaw, Poland
[d] Department of Adult Psychiatry, Poznan University of Medical Sciences, Szpitalna 27/33, 60-572 Poznan, Poland
[e] Department of Regenerative Medicine, Warsaw Medical University, Poland

ARTICLE INFO

Keywords:
Stem cell
Sphingosine-1-phosphate
VSEL
Bipolar disorder
Schizophrenia
Anxiety disorder
Complement cascade

ABSTRACT

The new area of research in psychiatric disorders is concerned with abnormal regeneration processes. The role of brain neurogenesis has been studied for decades. New discoveries, concerned with the pluripotency of VSEL cells and the role of factors involved in stem cell trafficking in peripheral blood create hope that it will be possible to develop a better understanding of the processes of neuroregeneration/neurodegeneration. There is an ongoing research investigating concentrations of: sphingosine -1-phosphate, SDF-1, elements of complement cascade, and stem cells in peripheral blood, including their possible connection to psychiatric disorders. Collected data, suggesting an abnormal course of regeneration processes in psychiatric disorders, raises hope of finding new potential markers of psychosis and anxiety disorders.

1. Introduction

Recent decades are the period of exceptionally intensive research on stem cells. Reservoirs of adult stem cells, characterized by high cell turnover and activity connected with self-renewal and differentiation into cells of different tissues, including regeneration of damages, are specific “niches” - bone marrow for hematopoietic system, hair follicles in the skin and the small intestine. (Rezza et al., 2014). Regeneration processes with the participation of stem cells remain under control of many paracrine and autocrine signals. Thanks to the work of Eriksson (Eriksson et al., 1998) we know that neurogenesis in adult human brain is also possible. This particular field is characterized by slow rate of cell turnover (Beckervordersandforth et al., 2010). Not all details are known in terms of signaling and specific markers of these stem cells. Since the formation of central nervous system, neurogenesis is precisely regulated during all stages, from proliferation to differentiation. The control of these processes in adult brain is just as precise. Brain-derived neurotrophic factor and vascular endothelial growth factor lower apoptosis in cultured neurons and stimulate neurogenesis (Li et al., 2014). In continued maturation of the brain, the number of neural stem cells radically falls. Those cells reside in the so-called “stem cell niches” of the central nervous system, and there are only 2 regions of the brain that with all certainty have the ability to generate new neurons in the adult life: the subventricular zone of the anterolateral ventricle (where the newly created cells migrate along the rostral migratory stream towards the olfactory bulb where they can differentiate into adult neurons), and the subgranular zone of the hippocampal dentate gyrus (where granule cells are created) (Lin and Iacovittin, 2015). Processes involved in neurogenesis remain under close surveillance of many factors, including genes such as: NeuroD1 (Gao et al., 2009), Prox1 (Karalay et al., 2011), Sox (Mu et al., 2012), Cdk5 (Jessberger et al., 2008), DISC1 (Duan et al., 2007) as well as Notch and Wnt signaling (Braun and Jessberger, 2014).

The possible role of the adult neurogenesis is assured by the relationship between this phenomenon and memory performance, first observed by van Praag (van Praag et al., 1999). The role of neurogenesis is often debated in neuropsychiatric disorders. After an injury, processes of neurogenesis, mainly – gliogenesis, are activated in other regions of the brain (Decimo et al., 2012).

Stem cells in peripheral blood and their possible role in neurogen-

Abbreviations: BP, bipolar disorder; C3a, C5a, activated complement cascade components; CNS, central nervous system; EPC, endothelial progenitor cell; ERK, extracellular signal-regulated kinase; HSC, hematopoietic stem cell; iPSC, induced pluripotent stem cell; LPA, lysophosphatidic acid; MSC, mesenchymal stem cell; PD, panic disorder; S1P, sphingosine-1-phosphate; SDF-1, Stromal Cell-Derived Factor 1; VSEL, Very Small Embryonic-Like Stem Cell

* Corresponding author.
E-mail address: samoj@pum.edu.pl (J. Samochowiec).

http://dx.doi.org/10.1016/j.pnpbp.2017.04.005
Received 12 January 2017; Received in revised form 28 March 2017; Accepted 5 April 2017
Available online 07 April 2017

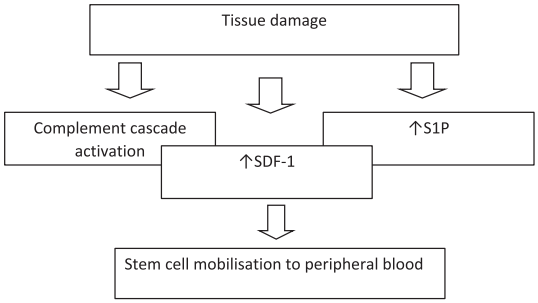

Fig. 1. The possible role of factors involved in stem cell trafficking (for details: Klich et al., 2010; Kim et al., 2015; Ratajczak et al., 2012).

esis are a new field of interest.

The databases MEDLINE/PubMed were searched for publications, from January 1, 2005 through January 15, 2017. We took into consideration publications written in English, relating to neurogenesis, stem cells, sphingosine-1-phosphate, complement cascade, SDF-1 in psychiatric disorders: depression, bipolar disorder, schizophrenia, anxiety disorder, substance dependence, anorexia nervosa. We excluded conference abstracts, case studies and other studies which were methodologically incorrect. A total of 83 publications were included (Fig. 1).

1.1. Depression

Despite great prevalence of depressive disorders and countless studies on the topic of depression, pathophysiology of depression is not fully known yet. From studies conducted on animals, specifically – on animal stress model, it emerges that stress, physical as well as psychosocial, is a factor suppressing neurogenesis in the hippocampus (Gould et al., 1997), which contributes to the appearance of cognitive symptoms of depression (Lucassen et al., 2010). However, antidepressants increase neurogenesis (Santarelli et al., 2003). Progressively, researchers highlight the significant role of exposure to stress during the early life. A trauma at that time of development can (re)program brain plasticity, increasing the risk of dementia and depression (Lucassen et al., 2015). In humans, it was observed that the volume of the hippocampus is significantly smaller in particular on the onset of depression, which is seen in data from meta-analyses - smaller grey-matter volume of the left hippocampus in experimental group as compared to control group (Sawyer et al., 2012; Wise et al., 2016). Antidepressants can potentially reverse reduction of hippocampal grey matter (Arnone et al., 2013). Ablating hippocampal neurogenesis causes no antidepressant activity in animal model response to these medications (Dranovsky and Hen, 2006). Reduction of neurogenesis leads to an increase of stress-induced anxiety/depression-like behavior in animals (Snyder et al., 2011). Electroconvulsive shock, constituting an animal model of electroconvulsive therapy in humans, induces hippocampal neurogenesis in mammals (Rotheneichner et al., 2014).

In depression, studies conducted on the role of stem cells outside the central nervous system are very scarce in number. They cover the relationship between bone marrow transplantation and depression (Baliousis et al., 2016). It is worth noticing the influence of emotions on mortality after adult stem cell transplant. If the patient's attitude before the surgery is positive, then the short-term prognosis is better. On the other hand, pre-transplant negative emotional profiles result in worse long-term prognosis (Hoodin et al., 2006).

1.2. Bipolar disorder

Bipolar disorder is a chronic polygenic disease, affecting 0,7–6% of population, in which clinical risk factors are early-onset panic attacks and disorder, separation anxiety, generalized anxiety disorders, conduct disorder, ADHD, impulsivity and criminal behavior (Faedda et al., 2014; Gibson, 2010). This disorder affects cognition, mood and affect and probably has a developmental character (McNamara et al., 2010), which is confirmed by neuroimaging studies (McDonald, 2015). The heritability is estimated to be at around 80–90% (McGuffin et al., 2003). Genetic studies reveal changes in genes engaged in the development of the central nervous system, including cell migration, extracellular matrix, H3K4 methylation, and calcium signaling (O'Shea and McInnis, 2016). Neurogenesis in BP is diminished, while effective pharmacotherapy leads to its growth (Schloesser et al., 2007). Stem cell factor plasma levels, both a hematopoietic growth factor and a neurotrophic factor, increase substantially in responders with major depression in the course of BP (Benedetti et al., 2016).

In combined case/control analysis and the family-based analysis, Xu (Xu et al., 2014) found association on 1q21.2 (closest gene: sphingosine-1-phosphate receptor 1 gene, S1PR1) for BP and for schizophrenia. While examining rat embryos and nervous cell lines, Harada (Harada et al., 2004) concluded that receptors for S1P are located in the areas of active neurogenesis. Moreover, the authors found mRNA for S1P1-3 and S1P5 receptors in progenitor nervous cells in the hippocampi of rat embryos. S1P causes a stimulation of transitional aggregation of hippocampal progenitor cells and, through the activation of G protein - a stimulation of ERK phosphorylation, DNA synthesis and proliferation of progenitor nervous cells. Hurst and al. found the expression of LPA and S1P receptors in cells of neuroepithelial lineage descendant from stem cells derived from the human embryo. LPA and S1P caused the induction of p44/42 ERK MAP kinase phosphorylation and stimulated proliferation of cells on path dependent on EGFR (Epidermal Growth Factor Receptor) as well as ERK and its temporary aggregation (Hurst et al., 2008).

Nowadays, research with the use of neurons reprogrammed from induced pluripotent stem cells (iPSC) points out the abnormalities in humans affected by BP in calcium signaling, endoplasmic reticulum stress response, mitochondrial oxidative pathway, membrane ion channels, circadian system and apoptosis related genes (Viswanath et al., 2015).

Ferensztajn-Rochowiak (Ferensztajn-Rochowiak et al., 2016) in their investigation of the effect of long-term lithium treatment on VSEL (Very Small Embryonic-Like Stem Cells), hematopoietic stem cells (HSC), mesenchymal stem cells (MSC) and endothelial progenitor cells (EPC) circulating in peripheral blood found that in BP subjects without lithium treatment the number of $CD34^+$ VSELs was significantly higher, and MSCs and EPCs numerically higher, than in control subjects and the number of $CD34^+$ VSELs correlated with the duration of the illness. The authors postulate the protective role of lithium, because these parameters do not differ between lithium-treated patients and controls. The addition to this study is, thus far unpublished, data concerning the factors involved in trafficking of stem cells. Peripheral blood concentration of C3a, C5a, C5b-9 and SDF-1 was significantly higher in BP group compared to control group. It is worth noticing that chronic activation of complement cascade can cause damage to cells, connected to etiopathogenesis of neurodegenerative disorders (Rubio-Perez and Morillas-Ruiz, 2012; Panaro and Cianciulli, 2012). The concentration of S1P does not distinguish BP patients from controls.

1.3. Schizophrenia

Schizophrenia is a severe chronic neurodevelopmental disease (Weinberger, 1987), albeit there is still proof of its neurodegenerative character. There are 12 chromosomal regions potentially connected with the etiology of schizophrenia, which contain 2181 known genes as well as 9 specific genes, among them protein coding genes potentially related to neurogenesis (Mura et al., 2012). DISC-1 gene, responsible for the development of the hippocampus as well as the regulation of neurogenesis in adult brain, exhibits association with schizophrenia (Schurov et al., 2004; Schumacher et al., 2009). In people affected by