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Stem cells and mechanisms regulating their trafficking – a new and challenging area of investigation in modern psychiatry

Mariusz Z. Ratajczak

Stem Cell Institute at the James Graham Brown Cancer Center, University of Louisville, Louisville, Ky 40202, USA and Department of Regenerative Medicine at Warsaw Medical University, Warsaw, Poland

Every century is characterized by scientific achievements that become historical landmarks, and most likely our current century will be remembered for its significant discoveries relating to stem cell research, including the understanding of human physiological regeneration, the pathological processes involving stem cells, and the mechanisms that regulate their trafficking in the body. This is a huge challenge, but there is hope that new therapies will be developed that enable us to treat several so-far-incurable diseases, which will prolong life span and improve our quality of life. To this end, we seek a better understanding of the diagnosis, prophylaxis, and treatment of psychiatric disorders. These challenges are topics of this special issue on Stem Cells in Psychiatric Disorders in *Progress in Neuro-Psychopharmacology & Biological Psychiatry*.

The introductory paper in this special issue discusses the types of embryonic and non-embryonic stem cells that are under consideration in regenerative medicine, including neurological diseases, their potential applications, and current ethical and technical limitations (Ratajczak et al., 2017a). We are still on a quest for the most efficient stem cell for clinical applications, searching for applicable pluripotent stem cells that have a broad potential to differentiate into cells belonging to the three germ layers. Unfortunately, both classical pluripotent stem cells, such as embryonic stem cells, and induced pluripotent stem cells (iPSCs) bear the risk of teratoma formation after injection into the host and, as recently demonstrated, exhibit problems related to genomic instability (Yoshihara et al., 2017). Therefore, the focus of interest here is on normal stem cells isolated from adult tissues. However, the question remains whether adult tissues also harbor other stem cells with much broader differentiation potential. This introductory paper also highlights two main goals of regenerative medicine, that is, i) to employ stem cells efficiently and safely in therapies for injured organs and tissues and ii) to develop strategies that will improve quality of life and longevity by improving the regenerative potential and proper functioning of adult stem cells residing in various organs, including the brain (Ratajczak et al., 2017b). It is not trivial to state that stem cells, which regulate proper functioning of the organism, have indirect effects on the condition of the human psyche.

In the next paper, Dr. Borlongan's group focuses on the neurodegeneration and resulting psychiatric symptoms observed in fetal alcohol spectrum disorder and epilepsy (Lippert et al., 2017). It is known that intrauterine exposure to alcohol damages the developing brain and may lead to defects in its development. This damage results after birth in long-term

cognitive, motor, and sensory impairment, resulting in pathological symptoms associated with many psychiatric disorders. As discussed in more detail by the authors, the alcohol-related disruptions of neural networks is characterized by impaired neurogenesis and precedes, accompanies, and possibly even exacerbates the evolution and progression of the symptoms of psychiatric diseases. The authors conclude that these alcohol-related developmental brain problems are candidate targets for future stem cell therapies.

In the following paper Dr. Samochowiec and coworkers (Kucharska-Mazur et al., 2017) summarize their work on the circulation of stem cells in peripheral blood (PB) and selected parameters regulating this phenomenon in patients with psychiatric and anxiety disorders. It is well known that stem cells are endowed with migratory potential and that they migrate during embryonic development and organogenesis. Later in adult life, a small percentage of hematopoietic stem cells (HSCs) as well as other types of stem cells, including mesenchymal stem cells (MSCs), endothelial progenitor cells (EPCs), and even the rare population of very small embryonic-like stem cells (VSELs), is continuously released from their stem cell niches into the peripheral blood (PB) in a process known as stem cell mobilization (Ratajczak 2015). The number of circulating HSCs and other types of non-hematopoietic stem cells increases in PB in response to i) systemic or local inflammation, ii) strenuous exercise, iii) stress, iv) tissue/organ injury, and v) pharmacological agents. Moreover, circulating HSCs and other stem cells undergo a circadian rhythm in their circulation in PB, with the peak occurring early in the morning and the nadir at night. The cyclical circadian release of HSCs is regulated by genes of the molecular clock through circadian noradrenaline secretion in a β 3-adrenergic receptor-dependent manner by the sympathetic nervous fibers that innervate bone marrow (BM) (Mendez-Ferrer et al., 2008) and diurnal changes complement cascade (ComC) and the coagulation cascade (CoaC) activity due to deep sleep hypoxia (Borkowska et al., 2016).

Mechanisms that govern mobilization of stem cells have been best studied so far in HSCs. It is known that i) chemokines (e.g., stromal-derived factor 1, SDF-1), ii) growth factors, iii) bioactive lipids (e.g., sphingosine-1-phosphate, S1P), iv) extracellular nucleotides, and v) activation of the ComC and CoaC govern trafficking of HSCs in the body. In parallel, evidence has accumulated that the same signals orchestrate trafficking of other non-hematopoietic stem cells, including MSCs, EPCs, and VSELs (Ratajczak 2015). Circulation of HSCs in PB may be envisioned as a process by which these cells relocate between distant BM stem cell niches in order to keep the total pool of BM stem cells in the body in balance. They may also play a role in patrolling peripheral tissues for potential signs of organ injury or inflammation. In addition to HSCs, other types of stem cells that circulate in PB may play a similar pro-regenerative role. As presented in the paper by Dr. Samochowiec's group (Kucharska-Mazur et al., 2017), an increase in the number of certain types of stem cells circulating in PB and factors that regulate their trafficking, such as SDF-1, S1P, and activation of the ComC, is observed in certain psychiatric disorders. Despite the fact that the role of postnatal brain neurogenesis and remodeling has been studied for decades, recent observations showing changes in stem cell trafficking in PB make it possible to shed new light on the processes of neuroregeneration and neurodegeneration. The authors announce the onset of a new era of research in psychiatric disorders with the possibility of affecting, by therapeutic means, altered or abnormal brain-regeneration processes. The data collected

so far raise hopes of finding new markers of psychosis and anxiety disorders as well as developing new stem cell-based treatment strategies. Further studies may allow stem cells and factors involved in their trafficking to be used as biomarkers or even as healing factors in psychiatric patients.

It is well known that some of the drugs employed in psychiatry, such as lithium, may mobilize stem cells to move into PB. This intriguing issue is discussed in the next paper in this special issue by Dr. Rybakowski's group (Rybakowski et al. 2017). In this interesting paper the authors summarize their work on markers of stem cell pluripotency and on glial cell markers in the PB of bipolar patients on long-term lithium treatment. These are provocative observations, and the potential effect of other drugs employed in psychiatry requires further study. On the other hand, it would also be interesting to see how electro- or insulin-shock therapies affect mobilization of these cells into peripheral blood and potentially enforces their trafficking between bone marrow and brain.

Experimental neurology and psychiatry are both searching for reliable experimental models with which to study psychiatric disorders, and this issue is well addressed in a comprehensive review by Dr. Ulrich's group (Correa-Velloso et al. 2017). The authors address pathophysiological events in the comorbidity of bipolar disorder (BD) and Alzheimer's disease that involve various pathological mechanisms, such as aberrant neurogenesis and neurotoxicity, and discuss current therapeutic approaches that, unfortunately, result in neurodegeneration and brain atrophy. The proper understanding of these complex mechanisms is crucial to proposing stem cell-based strategies for treatment and prevention of BD and Alzheimer's disease progression. Since it is extremely difficult to study the molecular basis of these disease progressions directly in patients, it is helpful to study in vitro patient-derived immortalized iPSCs, which may provide relevant information about the embryonic origins, intracellular signaling pathways, and molecular mechanisms involved in the pathogenesis of these disorders. Thus, iPSCs derived from the patient's own cells are helpful in understanding the pathogenesis of certain disorders and in developing and testing specific drugs.

The application of human iPSCs as a revolutionary tool for generation of tissue-relevant cell types exhibiting a patient's genetic and molecular background in disease modeling and drug discovery is discussed more extensively in the second paper from Dr. Ulrich's group (Liang et al., 2017). In that review, the authors present some major achievements in the neuroscience field using iPSC technology and discuss some promising perspectives for rapidly developing personalized medicine. These cells are also helpful in understanding the cellular and molecular basis of neurological disorders and are a leading model for discovery of new targets for potential drugs. Based on progress in this field, it is expected that iPSCs will enable advances in disease modeling for patient-specific prognosis, therapy evaluation, and cell replacement therapy in both neurological and psychiatric disorders.

Lastly, the very interesting paper contributed by Drs. Filipkowski and Kaczmarek discusses their own results in mice with cyclin D2 knockout (KO) (Filipkowski and Kaczmarek 2017). The inspiration for their work was the results reported by others in which new neurons are produced in the brains of adult mammals, and these neurons may potentially play a pivotal

role in learning and memory phenomena, mood control, and epileptogenesis (Eriksson et al. 1998). Based on their own research, the authors noticed, somewhat to their surprise, that severely impaired adult brain neurogenesis in cyclin D2-KO mice produces very limited phenotypic changes. Specifically, their studies revealed that cyclin D2-KO mice do not show major deficits in several behavioral paradigms assessing hippocampal learning and memory. Thus, this paper challenges the role of postnatal neurogenesis and proposes two new explanations for their findings. First, either there exists a so-far-undiscovered compensatory mechanism replacing the functions of newborn neurons, or the role of adult neurogenesis in the physiology of the brain has been greatly exaggerated. To resolve these challenging issues, further experimentation is needed.

In conclusion, this is, to our knowledge, the first special issue on stem cells in psychiatry published by *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. The contributors ask new and provocative questions that will serve as an invitation to more researchers to enter this still-somewhat-understudied area of research and regenerative medicine. Therefore, we expect new and exciting discoveries in this field in the near future. Stay tuned.

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