Progress in Neuropsychopharmacology & Biological Psychiatry 80 (2018) 3–9

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

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

Stem cells and their potential clinical applications in psychiatric disorders

Mariusz Z. Ratajczak[a,b,*], Andrzej K. Ciechanowicz[b], Jolanta Kucharska-Mazur[c], Jerzy Samochowiec[c]

[a] Stem Cell Institute, 500 South Floyd Street, James Graham Brown Cancer Center, University of Louisville, Louisville 40202, KY, USA
[b] Department of Regenerative Medicine Warsaw Medical University, Warsaw, Poland
[c] Department of Psychiatry, Pomeranian Medical University, Szczecin, Poland

ARTICLE INFO

Keywords:
Embryonic stem cells
Induced pluripotent stem cells
Adult tissue-derived stem cells
Paracrine effects
Extracellular vesicles
Very small embryonic like stem cells

ABSTRACT

The robustness of stem cells is one of the major factors that directly impacts life quality and life span. Evidence has accumulated that changes in the stem cell compartment affect human mental health and serve as an indicator of psychiatric problems. It is well known that stem cells continuously replace differentiated cells and tissues that are used up during life, although this replacement occurs at a different pace in the various organs. However, the participation of local neural stem cells in regeneration of the central nervous system is controversial. It is known that low numbers of stem cells circulate continuously in peripheral blood (PB) and lymph and undergo a circadian rhythm in their PB level, with the peak occurring early in the morning and the nadir at night, and recent evidence suggests that the number and pattern of circulating stem cells in PB changes in psychotic disorders. On the other hand, progress in the creation of induced pluripotent stem cells (iPSCs) from patient somatic cells provides valuable tools with which to study changes in gene expression in psychotic patients. We will discuss the various potential sources of stem cells that are currently employed in regenerative medicine and the mechanisms that explain some of their beneficial effects as well as the emerging problems with stem cell therapies. However, the main question remains: Will it be possible in the future to modulate the stem cell compartment to reverse psychiatric problems?

1. Introduction

For almost half a century the successful application of hematopoietic stem cells in hematopoietic transplants has encouraged attempts to employ stem cells in treating several other clinical problems, including i) damaged myocardium after heart infarction, ii) brain after stroke, iii) spinal cord after mechanical injury, iv) age-related macular degeneration (AMD) of retina, v) diabetes, vi) extensive skin burns, vii) damaged liver, and viii) Parkinson's disease (Altarche-Xifro et al., 2016; Bryukhovetskiy and Bryukhovetskiy, 2015; Cambria et al., 2016; Carvalho et al., 2015; Divani et al., 2007; Kasahara et al., 2016; Margini et al., 2014; Park et al., 2017; Rea et al., 2015). Unfortunately, beyond hematopoietic transplants, the clinical results for stem cell therapies have been rather disappointing, and several encouraging results initially reported in laboratory animals have not been reproduced in humans (Ratajczak et al., 2016a).

It is well known that low numbers of hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), endothelial progenitor cells (EPCs), and very small embryonic-like stem cells (VSELs) circulate continuously in peripheral blood (PB) and lymph and undergo a circadian rhythm, with the peak occurring early in the morning and the nadir at night (Giudice et al., 2010; Méndez-Ferrer et al., 2009). Moreover, the number of circulating HSPCs increases in PB in response to i) systemic or local inflammation, ii) strenuous physical exercise, iii) hypoxia, and iv) tissue or organ injuries (Bryukhovetskiy and Bryukhovetskiy, 2015; Cambria et al., 2016; Carvalho et al., 2015; Divani et al., 2007; Kasahara et al., 2016; Liu and Ratajczak, 2012; Serebrovskaya et al., 2011). An important role is played by activation of the complement cascade (ComC) in the release of stem cells into PB and lymph from their tissue niches (Janowska-Wieczorek et al., 2012). Recent evidence indicates that stem cells may also be involved in the pathogenesis of certain psychotic disorders (Ratajczak et al., 2014b), and in fact there are reports indicating that the number and circulation pattern of stem cell subtypes as well as factors involved in their egress into peripheral blood (e.g., ComC cleavage fragments) play an important role (Borkowska et al., 2016; Borkowska et al., 2014).

On the other hand, local stem cells residing in the stem cell niches in adult tissues are responsible for organ rejuvenation and the replace-

* Corresponding author at: Hoenig Endowed Chair, Stem Cell Institute, James Graham Brown Cancer Center, University of Louisville, 500 S. Floyd Street, Rm. 107, Louisville, KY 40202, USA.
E-mail address: mzrata01@louisville.edu (M.Z. Ratajczak).

http://dx.doi.org/10.1016/j.pnpbp.2017.04.020
Received 9 February 2017; Received in revised form 17 April 2017; Accepted 19 April 2017
Available online 20 April 2017

ment of senescent cells. However, this process occurs at a varying pace in different organs, and while hematopoietic cells, intestinal epithelium, and epidermis are continuously replaced by new cells, this process is very slow in other organs (e.g., heart or skeletal muscles), and its existence is still questioned for the central nervous system (Cerletti et al., 2008; Mackay-Sim, 2010; Ratajczak et al., 2016a).

Nevertheless, results showing changes in the pattern of circulating stem cells in peripheral blood (Giudice et al., 2010; Méndez-Ferrer et al., 2009) and recent indications that certain psychiatric disorders could be the result of brain restructuring (Ratajczak et al., 2014b) has raised interest in this topic among psychiatrists. While there is still a long way to go to fully understand these mutual relationships, this review is meant to give the reader a general overview on the current progress in, and limitations of, stem cell research.

2. Stem cells as a fountain of youth

The unique properties of stem cells that reside in tissues make them candidates for two important clinical applications. First, they could be employed in clinical settings to regenerate damaged tissues and improve the function of affected organs. These applications would require their isolation and ex vivo expansion followed by systemic or local delivery. Some investigators even envision that transplantation of entire organs will be replaced in the future by transplantation of a suspension of stem cells, alone or in combination with organic or synthetic scaffolds, that is able to establish a three-dimensional functional organ or at least a significant functional fragment (Alison and Islam, 2009; Kucia et al., 2005). This requires that tissue derived by such means is properly innervated and vascularized by blood and lymphatic vessels and responsive to external and internal stimuli. In other words, implanted stem cells should recapitulate embryonic development, but this requirement is still far from feasible technically.

Second, an even more important aspect of regenerative medicine is increasing stem cell robustness and regenerative potential directly in vivo in adult organisms by therapeutic means, including i) regular physical activity ii) caloric restriction, and iii) stem cell-targeted pharmacological interventions. It is known that regular physical activity increases the number of stem cells in adult tissues, including brain (Boppart et al., 2015; Grymula et al., 2014; Hell et al., 2012; Mazzoccoli et al., 2014; Marycz et al., 2016). Physical exercise is also known to increase the numbers of various stem cells circulating in PB and, on the other hand, also to ameliorate symptoms in psychotic patients (Marycz et al., 2016; Ratajczak et al., 2014b). Therefore, a direct link between the beneficial effect of physical activity, psychotic syndromes, and the level of stem cells circulating in PB requires follow-up studies. Similarly, psychotic effects are ameliorated under caloric restriction and loss of body weight, and it is well known that these approaches increase the robustness of the stem cell compartment (Borkowska et al., 2014; Grymula et al., 2014). Interestingly, lithium, which is one of the drugs commonly used in psychiatry, has been shown to mobilize stem cells and increase their number in PB (Ferensztajn-Rochowiak et al., 2016; Focosi et al., 2009; Qi et al., 2017). Finally, metformin, which is employed to reduce body weight in psychotic patients, increases the number of the most developmentally primitive stem cells, known as VSELs, in adult tissues (Marycz et al., 2016). However, this second preventive aspect of clinical regenerative medicine, in contrast to stem cell applications as therapeutics in emergency situations, is still somewhat underappreciated. In particular, this area awaits development of more specific drugs, in addition to metformin, that would increase stem cell robustness, and this provides a challenge to the development of stem cell-tailored pharmacology (Ferensztajn-Rochowiak et al., 2016; Focosi et al., 2009; Marycz et al., 2016; Qi et al., 2017; Ratajczak et al., 2014b).

3. Therapeutic application of stem cells isolated from adult tissues

Despite hype generated by the media, the truth is that adult stem cells are the only cells to be employed safely in regenerative medicine so far. However, despite promising animal data, their clinical efficacy in other than hematological applications is still untested. Several types of adult stem cells have been employed to treat certain clinical problems in cardiology, neurology, dermatology, gastroenterology, ophthalmology, and orthopedics (Atari et al., 2011; Cesselli et al., 2009; Kajstura et al., 2011; McGuckin et al., 2008; McGuckin et al., 2005; Virant-Klun et al., 2013). The most commonly used stem cells from adult tissues are isolated from bone marrow (BM), umbilical cord blood (UCB), umbilical cord, mobilized peripheral blood (mPB), adipose tissue, skin epithelium, myocardium, and skeletal muscle biopsies (Chen et al., 2016; Ho et al., 2011; Liu et al., 2015; Pringle et al., 2016; Ratajczak et al., 2012; Yang et al., 2010). As of today, no direct stem cell therapies are being performed in psychiatric patients. However, as we will discuss later, some of the drugs employed in psychiatry, such as lithium, may mobilize endogenous stem cells into PB (Ferensztajn-Rochowiak et al., 2016; Focosi et al., 2009; Qi et al., 2017; Ratajczak et al., 2014b), and some drugs, such as metformin, which is employed to reduce weight, also have a beneficial protective effect on the stem cell compartment (Marycz et al., 2016).

Unfortunately, in contrast to animal models, there is no solid and reproducible evidence in humans—despite several clinical trials—that these cells (except hematopoietic transplants) contribute to generating functional cells in damaged organs. In fact, the beneficial therapeutic effects of stem cells delivered to various tissues or organ during therapy are mostly related to their paracrine effects. To explain this finding, it is well known that stem cells, including those isolated from adult tissues currently employed in therapies, are a rich source of growth factors, cytokines, chemokines, and bioactive lipids that have i) trophic, ii) anti-apoptotic, and iii) pro-angiopoietic effects (Kim et al., 2013; Janowska-Wieczorek et al., 2001; Majka et al., 2001; Ratajczak et al., 2003). All of these factors have beneficial effects on damaged tissues. Moreover, in addition to soluble factors, stem cells also release membrane-derived extracellular microvesicles (ExMVs), ranging in size from 100 nm to 1 μm in diameter, which may deliver mRNA, miRNA, and functional proteins to target cells, thereby additionally promoting cell survival and proliferation (Ratajczak et al., 2016b; Ratajczak and Ratajczak, 2016c). Smaller ExMVs are also known as exosomes (Ratajczak et al., 2016b; Ratajczak and Ratajczak, 2016c). The evidence suggests that all these paracrine effects mediated by i) soluble factors and/or ii) by ExMVs are major factors responsible for the positive results observed in patients after systemic or local stem cell therapies (Ratajczak et al., 2016b; Ratajczak and Ratajczak, 2016c).

The best examples of the paracrine effects of stem cell therapies involve mesenchymal stromal cells (MSCs) isolated from bone marrow, adipose tissues, umbilical cord Wharton jelly, and recently even from dental pulp (Ribeiro et al., 2014). In the literature these cells have been wrongly termed “mesenchymal stem cells”, as only a very low percentage of these cells have the properties required for clonal growth and are real progenitors of connective tissue (Friedenstein et al., 1974); the bulk of these cells derived from expansion cultures are merely differentiated fibroblasts. MSCs are safe for clinical applications, easy to isolate, and grow in vitro (García-Gómez et al., 2010). Nevertheless, it is now well known that their beneficial effects are transient and mainly due to the release of soluble paracrine factors and ExMVs (Ratajczak et al., 2016a; Ratajczak et al., 2016b; Ratajczak and Ratajczak, 2016c). On the other hand, it would be interesting to study the composition of ExMVs, including soluble paracrine factors, protein, and mRNA, circulating in PB and released by MSCs in psychotic patients.