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Stem cells and their potential clinical applications in psychiatric disorders

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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?

Keywords

embryonic stem cells; induced pluripotent stem cells; adult tissue-derived stem cells; paracrine effects; extracellular vesicles

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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 replacement 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.

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; Mazzocchi 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; Oi 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; Oi et al., 2017; Ratajczak et al., 2014b).

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 (Ferenztajn-Rochowiak et al., 2016; Focosi et al., 2009; Oi 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 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 (ExMV), 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 et al., 2016c). (Smaller ExMVs are also known as exosomes (Ratajczak et al., 2016b; Ratajczak et al., 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 et al., 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 (Gracia-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 et al., 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.

The search for appropriate stem cells for potential therapeutic applications in regenerative medicine

The field of regenerative medicine is searching for ethically acceptable and efficient stem cells that could be employed for therapy (Ratajczak et al., 2014a). The ideal stem cells for application in regenerative medicine are pluripotent stem cells that, according to their definition, give rise to cells from all three germ layers (meso-, ecto-, and endoderm). Below, we will briefly discuss the currently available sources of pluripotent stem cells that have been proposed for clinical purposes.

Embryonic stem cells

Embryonic stem cell (ESC) lines are derived from early embryos at the blastula stage (Figure 1) (Ratajczak et al., 2014a). They can be generated from the blastula following the physiological process of fertilization (Figure 1A) or derived by employing a nuclear transfer strategy (Figure 1B). The blastula is an early embryonic stage which contains a group of pluripotent stem cells that are close to one of the poles inside its cavity that have the ability to differentiate into stem cells for all of the germ layers. These cells can be isolated and under appropriate culture conditions and become immortalized to proliferate as an established ESC line. ESCs derived from blastocysts, generated by the physiological process of fertilization as shown in Figure 1A, can be obtained from unused early embryos that are stored in liquid nitrogen at in vitro fertilization clinics. Unfortunately, generation of immortalized ESCs requires that the blastocyst be destroyed, and this strategy has been questioned from an ethical point of view. Besides ethical considerations, the problem with such ESCs is that they give rise to differentiated cells that have a unique combination of histocompatibility genes inherited from the sperm and egg and would be rejected by a histoincompatible recipient (Tachibana et al., 2013). This leaves the problem of finding a matched donor for the recipient of such cells. On the other hand, ESCs are difficult to control, as they may grow teratomas, and it is still a problem to obtain fully functional differentiated somatic cells from them (Cunningham et al., 2012). So far, no fully functional hematopoietic stem cells have been generated from ESCs (Ratajczak et al., 2016a; Ratajczak et al., 2004).

Another strategy is to create immortalized ESC lines from fertilized oocytes, which is known in the literature as therapeutic cloning (Ratajczak et al., 2016a; Ratajczak et al., 2011b; Tachibana et al., 2013). The first step in this strategy requires the insertion of a donor patient-derived nucleus isolated from a somatic cell into an enucleated oocyte derived from an ovulating female (Figure 1B). The patient-derived “bare” nucleus isolated from a differentiated somatic cell, when inserted into the cytoplasm of an enucleated oocyte, is re-differentiated by the plethora of enzymes, proteins, mRNAs, and miRNAs present in the oocyte cytoplasm to a state mimicking the nucleus in ESCs (Kramer et al., 2013; Ratajczak et al., 2012; Sanganalmath and Bolli, 2013; Tachibana et al., 2013). Such artificially created stem cells (called, in contrast to the physiologically fertilized oocyte zygote, a clonote) have the potential for development into a blastocyst and can be employed to obtain ESC lines from the inner cell mass of the blastocyst. What is most important, since the nucleus of the patient donor cell encodes all of the histocompatibility genes, it is possible to create

“tailored” ESCs that potentially would not be rejected by the patient’s immune system. Nevertheless, there are serious ethical concerns with this method, including the risk of teratoma formation, that are similar to those raised for ESCs isolated from blastocysts obtained by physiological fertilization. As a result of these concerns and technical obstacles, no further progress has been made, and this potential source of pluripotent stem cells has been abandoned (Cunningham et al., 2012). This strategy of using embryos created by nuclear transfer implanted into the uterus may also lead to so-called reproductive cloning (McHugh, 2004), which was employed, for example, in cloning Dolly the sheep (McHugh, 2004). What is very problematic: therapeutic cloning can also be made to work in humans, as recently demonstrated (Ratajczak et al., 2014a; Tachibana et al., 2013), and this creates a serious ethical danger surrounding any attempts to perform reproductive cloning in human beings.

Induced pluripotent stem cells

As mentioned above, strategies to obtain pluripotent stem cells using human oocytes to create embryos have become highly controversial from an ethical point of view. Therefore, an alternative strategy has been developed to obtain cells with multi-germ layer differentiation potential by ex vivo induction (transformation) of postnatal adult somatic cells into the embryonic stem cell state (Figure 2A). The target population of cells used for this reprogramming is isolated from normal adult tissues (e.g., skin fibroblasts) (Kramer et al., 2013; Sanganalmath and Bolli, 2013). Stem cells generated by genetic reprogramming (transformation), termed induced pluripotent stem cells (iPSCs), can differentiate into a wide spectrum of tissues. The initial strategy for obtaining iPSCs was based on the transduction of somatic fibroblasts with a set of four genes (Oct3/4, Sox2, c-Myc, Klf4), that encode transcription factors governing pluripotency and the resulting proliferation of embryonic cells (Kramer et al., 2013). What was most important, this technology allowed PSCs to be obtained that are histocompatible with the initial donor cell used for reprogramming. Unfortunately, several limitations have been identified for these cells, including the risk of teratoma and cancer formation. Recent evidence indicates that iPSCs have a significant problem with i) genomic, transcriptional, and epigenetic instability (Blasco et al., 2011; Yoshihara et al., 2016), ii) the risk of insertional mutagenesis (Blasco et al., 2011), iii) the immune response, even to autologous iPSCs (Zhang et al., 2015), iv) variability in differentiation capacity (Blasco et al., 2011), and v) significant variability among iPSC clones derived from the same donor cells (Blasco et al., 2011; Yoshihara et al., 2016). These limitations explain why the first clinical trials using these cells, which had been regarded as “promising” cells, were suspended (Ratajczak et al., 2016a).

In response to these obstacles, some attempts to mitigate the risk of therapies using iPSCs have been proposed. The risk of mutagenesis in iPSCs is based on the fact that the genes employed for the induction of pluripotency (Oct3/4, Sox2, c-Myc, Klf4) integrate randomly into the chromosomes of manipulated cells and, if incorporated into chromosome “hot spots”, could trigger activation of oncogenes or inactivate anti-oncogenes by insertional mutagenesis (Menon et al., 2016). To mitigate this possibility, several alternative strategies have been proposed, such as i) employing non-integrating DNA plasmids (Menon et al., 2016; Woodard and Wilson, 2015), ii) replacing DNA sequences with mRNA or miRNA

(Warren et al., 2010), iii) employing protein products in the form of cell-penetrating Oct3/4, Sox2, c-Myc, and Klf4 proteins instead of the genomic DNA itself (Li et al., 2011; Takahashi and Yamanaka, 2006), and even employing small molecules that modify the DNA structure of target cells and induce the pluripotent state (Li et al., 2011). Other strategies to mitigate the potential risks of iPSC therapy include i) the use of suicide genes to eliminate any remaining undifferentiated and highly proliferative iPSCs from the recipient's body after therapy (Kiuru et al., 2009) ii) the selection of a proper source of cells that are free of mutation prior to immortalization by transduction (Fujimori et al., 2016), iii) employing better gene delivery methods for reprogramming, such as using non-integrating vectors, Sendai virus, or episomal plasmid vectors, and iv) requiring a lower passage number for iPSCs, since mutations may accumulate in cells during passaging (Fusaki et al., 2009).

Based on these concerns, until significant progress is achieved in increasing the clinical safety of iPSCs, these cells can serve only as experimental models to study cell differentiation processes or as tools to identify the genes responsible for the origin of certain disorders. For example, they are being employed to generate cell lines from patients with psychotic disorders. However, even in this potential setting, we have to cautiously evaluate the data obtained using iPSCs because of their genomic instability and variability (Yoshira et al., 2016).

Potential pluripotent stem cells isolated from adult tissues

Evidence has accumulated that adult tissues harbor a population of very rare stem cells with pluripotent stem cell characteristics that express early-development embryonic markers. These cells were named very small embryonic-like stem cells (VSELs) (Figure 2B). However, other investigators also isolated similar cells, and, depending on the strategy by which they were isolated or cultured ex vivo, these cells have been given different names. Examples of such cells include multipotent adult stem cells (MASCs) (Beltrami et al., 2007), multilineage-differentiating stress-enduring (Muse) cells (Kuroda et al., 2013; Wakao et al., 2011), multipotent adult progenitor cells (MAPCs) (Jiang et al., 2002), unrestricted somatic stem cells (USSCs) (Kögler et al., 2004), marrow-isolated adult multilineage-inducible (MIAMI) cells (D'Ippolito et al., 2004), multipotent progenitor cells (MPCs) (Beltrami et al., 2007; Cesselli et al., 2009), and spore-like stem cells (Vacanti et al., 2001). However, these rare types of stem cells, which are able to change germ layer commitment, have never been well characterized at the single-cell level (Ratajczak et al., 2014a). Since it is rather unlikely that so many primitive stem cells exist independently in adult tissues, we believe that these stem cells are most likely closely related and represent overlapping populations of cells. By contrast, VSELs are very well characterized at the single-cell level, and we envision that they are at the top of the hierarchy of all these overlapping stem cell populations that have been identified in adult tissues (Kucia et al., 2006; Suszyńska et al., 2014). The presence of VSELs in adult tissues can be explained by the possibility that, early in embryogenesis, not all stem cells differentiate into tissue-committed stem cells, but some survive in developing organs as a dormant backup population of primitive stem cells—identified as VSELs—in postnatal tissues (Shin et al., 2010). VSELs can be envisioned as a quiescent backup population for tissue-committed stem cells. These small cells are detected in increasing numbers in peripheral blood (PB) during tissue or organ injuries (e.g., heart

infarct, stroke, intestinal inflammation, or skin burns) and, what is most interesting, also in certain psychotic disorders (Ratajczak et al., 2011a). The change in their number in PB and the meaning of their presence in the PB of psychiatric patients requires further study (Ratajczak et al., 2014b).

Stem cells in psychiatry—an emerging new field

Stem cells have already had an impact on several areas of clinical medicine, and psychiatry is no exception. There is now encouraging evidence that changes in the level of stem cells circulating in PB and factors that direct their trafficking, such as complement cascade cleavage fragments (Borkowska et al., 2016; Borkowska et al., 2014) or bioactive phospho-sphingolipids (Adamiak et al., 2015; Karapetyan et al., 2013, Ratajczak et al., 2016d), may be employed as diagnostic tools in psychiatry. Figure 3 summarizes progress and our understanding of this process. In steady state conditions there are always detectable at very low level some stem cell circulating in peripheral blood including population of hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), endothelial progenitor cells (EPCs) as well as rare VSELs (Figure 3A). The number of these cells increases in peripheral blood in stress and pathological situations related to tissue damage. As postulated (Kucharska-Mazur et al., 2017) the blood plasma level of potential chemoattractants (e.g., S1P, SDF-1) and trafficking modulators (e.g., C3a, C5a) for these cells increases in psychotic disorders leading to release of stem cells from bone marrow into circulation (Figure 3B). The pattern of released cells as well as chemoattractants in peripheral blood differs between various disorders and may be helpful as a diagnostic tool. Nevertheless, further studies are needed to see if these cells may play a role in brain tissue remodeling and if their level in peripheral blood is of prognostic value. It would be also interesting to see how pharmacological as well as other types of treatment in psychotic patients such as electro- or insulin-shock therapies affect mobilization of these cells into peripheral blood and potentially enforces their trafficking between bone marrow and brain.

To shed light on some of these questions in this special issue of *Progress in Neuropsychopharmacology & Biological Psychiatry* there are papers that address the potential role of stem cells circulating in PB as diagnostic and prognostic markers of psychotic disorders. In this issue, the current status of research on neural stem cells as well as potential applications of iPSCs in understanding the pathogenesis of certain neurological disorders are also discussed.

There is no doubt that this research area, encouraged by exciting initial clinical reports, will expand, and we can expect many interesting findings in the coming years. However, the question of whether stem cells will find direct application in treating psychotic patients is still open. Nevertheless, the fact that several treatment procedures currently in place using certain drugs (e.g., lithium) (Ferensztajn-Rochowiak et al., 2016; Focosi et al., 2009; Oi et al., 2017), therapies based on the application of metformin (Ratajczak et al., 2014a), and regular exercise therapy (Boppart et al., 2015; Marycz et al., 2016) have an impact on the stem cell compartment in psychotic patients justifies further studies in this area.

Conclusions

There is no doubt that stem cell therapies are the future of clinical medicine. However, news stories published by nonprofessional media predicting that clinical applications for a variety of medical problems will soon be available fosters premature and often unrealistic expectations in the public. Serious problems hampering progress in the field include patent issues and the financial involvement of biotechnology companies, which are frequently driven by competition, to the exclusion of cooperation.

The ethical concerns that have emerged around stem cells isolated from human embryos are somewhat muted, as these cells will not be employed in the clinic in the foreseeable future because of the risk of teratoma formation. Similarly, problems have emerged with iPSCs because of the genomic instability of these cells, and in this review we have tried to cool overheated expectations for the clinical application of these cells (Blasco et al., 2011; Ratajczak et al., 2014a; Yoshihara et al., 2016; Zhang et al., 2015). We also addressed the current state of adult stem cell therapies that, except in the hematological field, are mainly based on paracrine and trophic effects that increase survival and regeneration of damaged organs (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). Nevertheless, the identification of developmentally primitive VSELs residing in adult tissues and promising evidence that these cells can be isolated and expanded ex vivo (Kucia et al., 2006; Ratajczak et al., 2011a; Shin et al., 2010) opens the door to a new chapter in regenerative medicine. There is also no doubt that, along with stem cells and their potential clinical applications, a new chapter will be written in modern psychiatry.

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Highlights

- 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.
- However, the main question remains: Will it be possible in the future to modulate the stem cell compartment to reverse psychiatric problems?

Figure 1. ESCs obtained from embryos by physiological fertilization of the oocyte by sperm or after nuclear transfer of a somatic nucleus into an enucleated oocyte

A. ESCs isolated from blastocysts derived from an oocyte fertilized by sperm (a zygote). **B.** ESCs can also be obtained by means of therapeutic cloning as the result of transfer of the nucleus from an adult somatic cell (e.g., the nucleus of a fibroblast) into an enucleated oocyte. A totipotent stem cell generated by this strategy is called a clonote, which, like a zygote, gives rise to a blastocyst. Clonote-derived blastocysts, like zygote-derived blastocysts, are then a source of ESCs.

Figure 2. PSCs obtained from postnatal tissues

A. PSCs can also be obtained by transforming somatic cells (for example fibroblasts) using genes that encode embryonic transcription factors (e.g., Oct-4, Nanog, Klf-4, and c-myc). As mentioned in the text, there are also alternative strategies that replace DNA with mRNA, proteins, or regulatory miRNA and even with small-molecule modifiers of DNA. **B.** PSCs can also be obtained from the tissues of mature individuals (e.g., very small embryonic-like stem cells, also known as VSELs). With advances in expansion strategy, these cells could soon become real game changers in regenerative medicine.

Figure 3. Proposed concept of stem cell trafficking between bone marrow and brain in steady state conditions and psychotic disorders

A. In steady state conditions stem cells including hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), endothelial progenitor cells (EPCs) as well as rare population of VSELs circulate in peripheral blood at very low level. **B.** The number of these cells increases in peripheral blood in stress and pathological situations increases in response to chemoattractants (e.g., sphingosine-1 phosphate; S1P or stromal derived factor-1; SDF-1) as well as stem cell trafficking modulators (e.g., complement cascade cleavage fragments C3a and C5a) that are released from damaged brain.